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[2+4] Cycloaddition Reactions of 4-Nitro-3-phenylisoxazole with Carbo- and Heterodienes

Stefania Turchi,* Donatella Giomi, and Rodolfo Nesi*

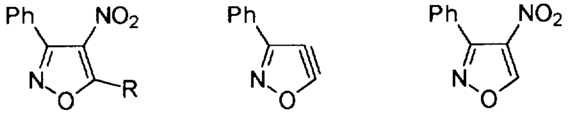
Dipartimento di Chimica Organica 'Ugo Schiff' dell'Università - Centro di Studio del CNR sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Via Gino Capponi 9, I-50121 Firenze, Italy

Paola Paoli

Dipartimento di Energetica dell'Università, Via di Santa Marta 3, I-50139 Firenze, Italy

Abstract: The title compound **4** reacted as a dienophile with open-chain and cyclic carbodienes as well as the 1-azadiene **16**, to yield different polynuclear isoxazole systems. On the contrary, it gave rise preferentially to a Michael-type reaction with the dimethyluracil derivative **19** affording the *cine*-substitution product **23**, whose structure was determined by an X-ray analysis. Some mechanistic features and synthetic opportunities are emphasized.

Recent results from our laboratory evidenced a novel facet of isoxazole chemistry: namely, the activated C(4)-C(5) double bond of the aromatic difunctionalized 4-nitro derivatives **1** and **2** was found to undergo Diels-Alder reactions with 2,3-dimethylbuta-1,3-diene (DMB), isoprene and cyclohexa-1,3-diene;[1] on the other hand, the same products behave as synthetic equivalents of the corresponding didehydro derivative **3** with the first diene since the activating groups can be easily removed from the corresponding adducts by different reductive elimination patterns (Figure 1).[2]



1 R=CO_2Et
2 R=COPh

3

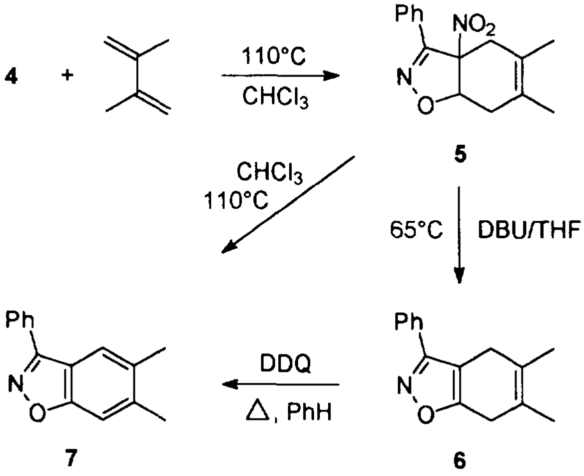
4

Figure 1

In order to expand the scope of these cycloaddition processes and with the aim to establish if the second electron-withdrawing group at position 5 plays a critical role for the dienophilic properties of the above heterocyclic system, we decided to explore the behaviour of **4** towards different 4π components.

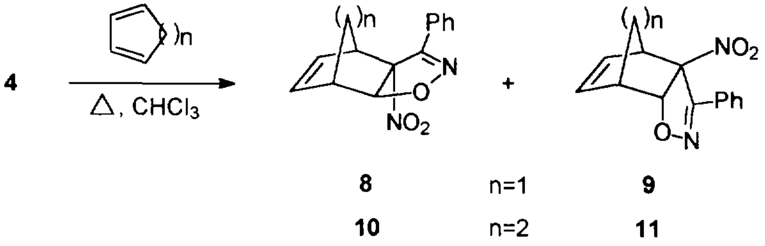
RESULTS AND DISCUSSION

Treatment of **4** with an excess of DMB in chloroform at 110°C afforded, together with some unreacted starting material and a trace amount of compound **7**, the bicyclic derivatives **5** and **6** that were isolated in 49% and 37% yields, respectively.



Scheme 1

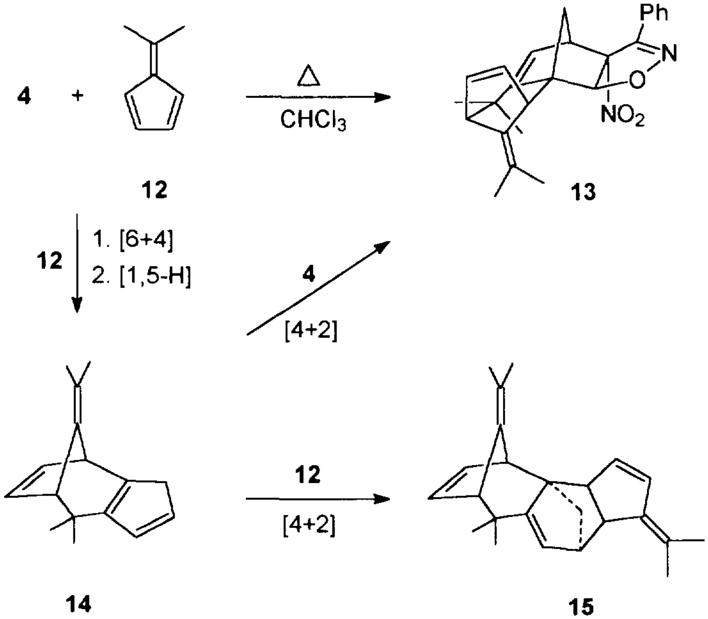
The primary cycloadduct **5** partially suffers from extrusion of nitrous acid to give **6** that was also obtained in very good yield from the same precursor and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under milder conditions; on the other hand, both compounds **5** and **6** were easily converted into the 1,2-benzisoxazole **7** by prolonged heating in the same solvent and oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), respectively (Scheme 1).



Scheme 2

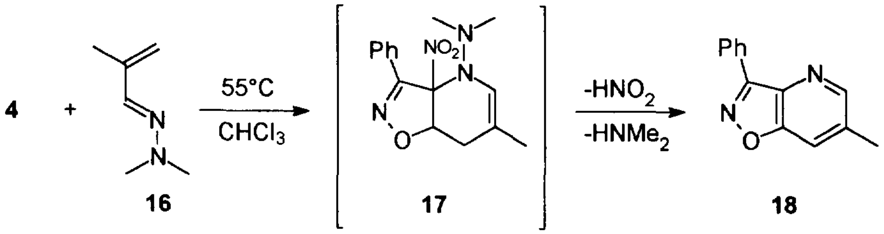
The same nitroisoxazole **4** entered as a dienophile in a Diels-Alder reaction with cyclopentadiene even at 40°C, and the resulting diastereomeric tricyclic adducts **8** and **9** were separated chromatographically in 41% and 29% yields, respectively; when the above reagent was replaced with cyclohexa-1,3-diene, a mixture of compounds **10** and **11** was obtained under more forcing conditions (Scheme 2).

The reactivity of **4** towards 6,6-dimethylfulvene **12** appeared less straightforward: whereas the nitro compound was substantially inert at 70°C, it reacted at higher temperature affording in good yield the polycyclic system **13**, whose formation was accounted for on the basis of the thermal behaviour of **12** previously investigated by a Swiss group.[3]



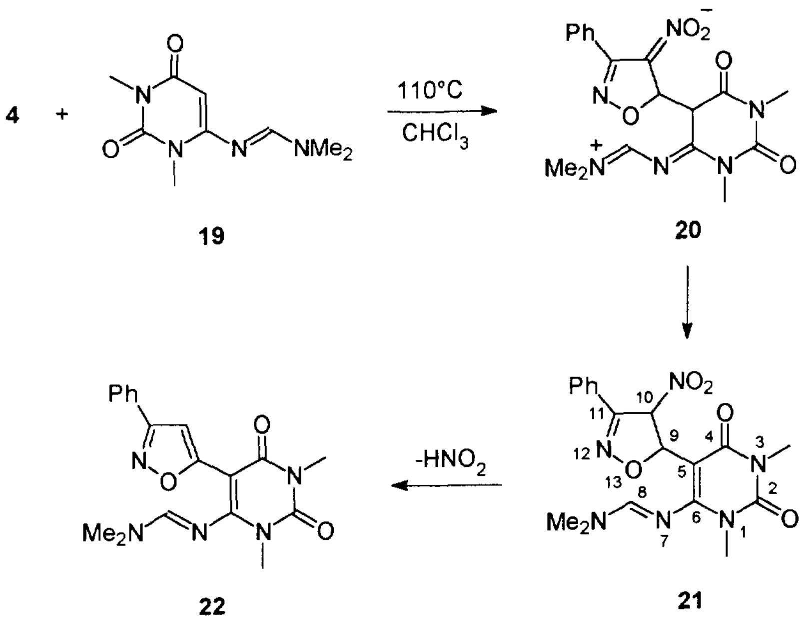
Scheme 3

Since the above diene was slowly converted by prolonged heating at 40°C into the trimer **15** through the key intermediate **14**, it seems reasonable that the latter species, better arising from **12** under our conditions, can be easily trapped by **4** into the final product *via* an alternative [4+2] cycloaddition (Scheme 3). Due to electronic and steric effects, this process was characterized both by a remarkable regiocontrol and an *endo/sin* selectivity with respect to the NO_2 group of **4** and the isopropylidene moiety of **14**, respectively.



Scheme 4

When the nitro derivative **4** was allowed to react with the 1-azadiene **16**, the isoxazolo-pyridine **18** was obtained in 59% yield by concomitant spontaneous loss of nitrous acid and dimethylamine from the unstable adduct **17** (Scheme 4).



Scheme 5

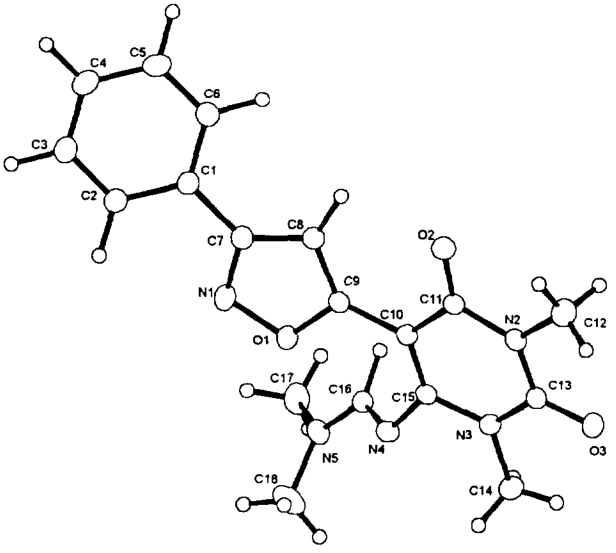
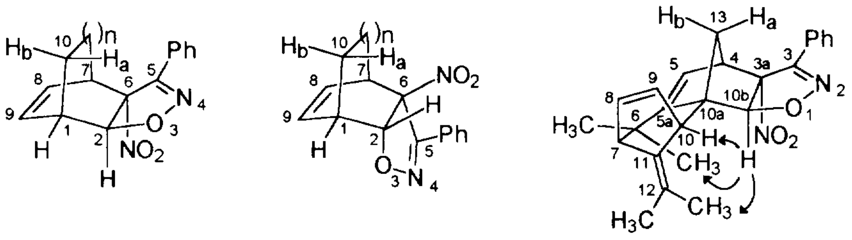


Figure 2. ORTEP drawing of **22**. Selected bond lengths (Å) and angles (°): C(1)-C(7) 1.472(3), C(7)-N(1) 1.311(3), C(7)-C(8) 1.410(3), C(8)-C(9) 1.351(3), C(9)-O(1) 1.360(3), C(9)-C(10) 1.453(3), O(1)-N(1) 1.404(3); N(1)-C(7)-C(8) 111.4(2), N(1)-C(7)-C(1) 120.1(2), C(8)-C(7)-C(1) 128.5(2), C(9)-C(8)-C(7) 105.7(2), C(8)-C(9)-O(1) 108.3(2), C(8)-C(9)-C(10) 133.3(2), O(1)-C(9)-C(10) 118.4(2), C(9)-O(1)-N(1) 109.3(2), C(7)-N(1)-O(1) 105.4(2).

Although the functionalized 1,3-dimethyluracil **19** was found to behave as a 2-azadiene partner with electrophilic alkenes in the synthesis of fused pyrido-pyrimidine systems,[4] attempts to apply the same strategy to **4** gave unsatisfactory results: indeed, a very complex reaction mixture arose from these reagents at 110°C and the predominant component (20% yield) was unambiguously identified as the isoxazole derivative **22** [5] by an X-ray structure determination (Figure 2).

According to the behaviour of 4-nitroisoxazoles with nucleophiles,[6] the preferential formation of this compound, that can be regarded as a *cine*-substitution product, is certainly due to an addition-elimination process involving in the first step a nucleophilic attack of the C-5 carbon of **19** on the 5-position of **4**; the resulting Michael adduct **20** then evolves into **22** through the intermediate Δ^2-isoxazoline **21** that could be isolated under milder conditions and converted by prolonged heating into the same final product (Scheme 5).

The structures of the new isoxazole polycyclic derivatives **5**, **8-11**, **13**, and **18** followed from analytical and spectral evidence (Experimental Section).



8 n=0 **9**

10 n=1 **11**

13

Figure 3

In particular, the relative stereochemistry of the NO_2 *endo* adducts **8** and **10** and the *exo* isomers **9** and **11** was determined on the basis of diagnostic differences shown by their ^1H NMR spectra for the H-2 resonance, easily identified in the range δ 5.08-5.67.

Whereas the patterns of the latter products were characterized by well resolved doublets ($J_{1,2}$ = 4.0 and 3.4 Hz, respectively), the *endo* proton of **8**, weakly coupled with H-1 and Hb-10, gives rise to a slightly structured signal masking a doublet of doublets ($J_{1,2}$ = 0.5-1.0 Hz, $J_{2,b10}$ = 1.6 Hz) as revealed by double resonance experiments; the former interaction increases remarkably on going from **8** to **10** and a doublet of triplets ($J_{1,2}$ = 4.0 Hz, $J_{2,7}$ = $J_{2,b10}$ = 1.0 Hz) was observed for the corresponding atom (Figure 3).

The structure of the polycyclic system **13** was also inferred from complementary ^1H NMR data by the following considerations:

(a) The assignement of the stereo- and regiochemistry of the isoxazoline ring was simply achieved from the shape of the H-10b resonance at δ 5.14: it appears as a doublet ($J_{10b,b13}$ = 1.0 Hz) that collapses to a singlet by irradiation of the 13-CH_2 multiplet at higher field, indicating an *endo* configuration for this proton. On the other hand, the lack of any coupling between the latter and H-4, confirmed by homonuclear correlation analysis, ruled out the alternative regioisomer.

(b) The *anti* geometry of the isopropylidene group with respect to the methylene bridge was deduced on the basis of a n.O.e. difference spectrum: indeed, irradiation of the H-10b signal caused, besides positive effects on H-10 and a 6-CH_3 group, a diagnostic enhancement for a methyl resonance of the above moiety at δ 1.89.

Finally, the regiochemistry of the binuclear derivative **18**, due to the control exerted by the NO_2 group of **4** on the cycloaddition, followed from the C-3a and C-7a NMR frequencies showing that these atoms are linked to a nitrogen and a carbon of the pyridine ring, respectively.[7]

The above findings clearly show that the 4-nitroisoxazole system with the free 5 position behaves as an attractive dienophile and some data on the reactivity of **4** (Schemes 1 and 4) appear encouraging since it can be regarded as a synthetic equivalent of the corresponding hetaryne **3** with 4π partners for direct six-membered carbo- and hetero-annulations of the isoxazole system; the possibility of applying this strategy, based on tandem [2+4] cycloaddition and elimination processes, to other nitro heterocycles [8] will be thoroughly investigated.

EXPERIMENTAL SECTION

Genaral Procedures. Melting points were taken on a Büchi 510 apparatus and are uncorrected. IR spectra were measured as KBr pellets with a Perkin-Elmer 881 spectrophotometer, while ^1H- and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions with a Varian Gemini-200 instrument operating at 200 MHz and 50 MHz, respectively: chemical shifts are expressed in ppm (δ) and coupling constants in Hertz (Hz). The relative assignement of the ^{13}C resonances was achieved by the use of coupled spectra and long-range heteronuclear correlation experiments. Elemental analyses were obtained by a Perkin-Elmer 240C Analyzer. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230-400 mesh) were used for TLC and flash chromatography, respectively; 30-50°C and 40-70°C petroleum ether were employed for crystallizations and chromatographic workup, respectively.

All the reactions of the nitroisoxazole **4** [9] (1 mmol) were carried out in a sealed tube (Pyrex N. 13) with an excess of the diene in $CHCl_3$ (1 ml) and the raw product, left by evaporation to dryness under reduced pressure, was subjected to flash chromatography; when the conversion of **4** was incomplete, the yields of the isolated compounds were determined on the basis of the recovered starting material.

Reaction of Compound 4 with DMB. The residue obtained by treatment of **4** with the diene (0.41 g, 0.56 ml, 5 mmol) at 110°C for 24 h was resolved into four components with petroleum ether/AcOEt (15:1 v/v) as eluent; after the fastest moving bands afforded a small amount of the benzisoxazole 7 [2] (R_f = 0.53, 0.005 g) and the dihydro derivative **6** [1b] (R_f = 0.48, 0.065 g, 37%), respectively, the third one gave (3a*SR*, 7a*RS*)-5,6-dimethyl-3a-nitro-3-phenyl-3a,4,7,7a-tetrahydro-1,2-benzisoxazole (**5**) (R_f = 0.40, 0.106 g, 49%) that was crystallized from hexane as white needles, m.p. 81-81.5°C; IR ν 1546, 1361 cm^{-1} (NO_2); ^1H NMR δ 1.62 (br s, 3H, 5-CH_3/6-CH_3), 1.77 (br s, 3H, 6-CH_3/5-CH_3), 2.32-2.63 [m (AB part of an ABX system), J_{AB} = 15.7 Hz, J_{AX} = J_{BX} = 5.5 Hz, 2H, 7-CH_2], 2.93 (AB system, J_{AB} = 15.5 Hz, 2H, 4-CH_2), 5.22 [t (X part of an ABX system), J_{AX} = J_{BX} = 5.5 Hz, 1H, H-7a], 7.35-7.55 (m, 5H, Ph); ^{13}C NMR δ 18.7 (q, 5-CH_3/6-CH_3), 19.1 (q, 6-CH_3/5-CH_3), 34.5 (t, C-4/C-7), 35.2 (t, C-7/C-4), 88.4 (d, C-7a), 103.1 (s, C-3a), 124.4 (s, C-6), 126.1 (s, C-5), 126.6 (s), 126.9 (d), 129.0 (d), 130.6 (d) (Ph), 153.4 (s, C-3). Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.41; H, 6.14; N, 10.38.

The unreacted **4** (R_f = 0.33, 0.04 g) was recovered from the following fractions.

Conversion of the Nitro Derivative 5 into 6. A solution of **5** (0.09 g, 0.33 mmol) and DBU (0.151 g, 0.148 ml, 0.99 mmol) in THF (1 ml) was stirred at 65°C for a week. Evaporation to dryness left a residue which was treated with water (5-10 ml), made weakly acidic with concentrated HCl, and extracted with ether (2x10 ml); removal of the solvent gave a gummy yellow product containing, together with small amounts of 7 and **5** (^{1}H NMR), the dihydrobenzisoxazole **6** that was isolated operating as above (0.055 g, 74%).

5,6-Dimethyl-3-phenyl-1,2-benzisoxazole (7).

From 5. A solution of **5** (0.05 g, 0.18 mmol) in $CHCl_3$ (1 ml) was heated in a sealed tube at 110°C for 60h; the sticky residue left by removal of the solvent was mixed with sand and sublimed at 50-60°C, 10^{-2} mmHg to give 7 (0.033 g, 80%).

From 6. A mixture of **6** (0.085 g, 0.38 mmol) and DDQ (0.095 g, 0.42 mmol) in anhydrous benzene (1 ml) was refluxed with stirring for 30 min, cooled, and filtered; the brown solid obtained by evaporation to dryness of the filtrate, was subjected to flash chromatography (toluene) to yield 7 ($R_f = 0.57$, 0.069 g, 82%).

Cycloaddition of 4 with Cyclopentadiene. Chromatographic workup [toluene/ligroin (5:1 v/v)] of the raw product obtained by treatment of **4** with the diene (0.792 g, 12 mmol) at 40°C for 6 days, afforded (2*SR*, 6*RS*)-6-nitro-5-phenyl-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]deca-4,8-diene (**8**) (R_f = 0.49, 0.105 g, 41%) that was crystallized from petroleum ether as a white solid, m.p. 56-57°C; IR ν 1543, 1352 cm^{-1} (NO_2); ^{1}H NMR δ 1.77-1.91 (AB system, J_{AB} = 10 Hz, 2H, 10-CH_2), 3.48 (m, 1H, H-1), 3.79 (m, 1H, H-7), 5.22 (sbr s, 1H, H-2), 6.23 (dd, $J_{8,9}$ = 5.7 Hz, $J_{1,9}$ = 3.3 Hz, 1H, H-9), 6.52 (dd, $J_{8,9}$ = 5.7 Hz, $J_{7,8}$ = 2.9 Hz, 1H, H-8), 7.40-7.43 (m, 3H, Ar-3H), 7.74-7.76 (m, 2H, Ar-2H); ^{13}C NMR δ 44.1 (t, C-10), 47.7 (d, C-7), 50.3 (d, C-1), 95.3 (d, C-2), 112.6 (s, C-6), 126.2 (s), 126.4 (d), 129.0 (d), 130.8 (d) (Ph), 135.2 (d, C-9), 138.1 (d, C-8), 151.4 (s, C-5). Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.85; H, 4.84; N, 10.86.

The following fractions gave (2*RS*, 6*SR*)-6-nitro-5-phenyl-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]deca-4,8-diene (**9**) (R_f = 0.38, 0.075 g, 29%) as white needles, m.p. 79.5-80°C (from pentane); IR ν 1535, 1337 cm^{-1} (NO_2); ^{1}H NMR δ 1.91-2.09 (AB system, J_{AB} = 10 Hz, 2H, 10-CH_2), 3.42 (m, 1H, H-1), 4.17 (m, 1H, H-7), 5.66 (d, $J_{1,2}$ = 4.0 Hz, 1H, H-2), 6.10 (dd, $J_{8,9}$ = 5.5 Hz, $J_{7,8}$ = 3.1 Hz, 1H, H-8), 6.36 (dd, $J_{8,9}$ = 5.5 Hz, $J_{1,9}$ = 2.8 Hz, 1H, H-9), 7.38-7.47 (m, 3H, Ar-3H), 7.60-7.65 (m, 2H, Ar-2H); ^{13}C NMR δ 46.5 (d, C-1), 47.9 (t, C-10), 51.0 (d, C-7), 95.5 (d, C-2), 110.5 (s, C-6), 126.1 (d), 126.4 (s), 129.1 (d), 130.7 (d) (Ph), 133.5 (d, C-8), 137.6 (d, C-9), 152.1 (s, C-5). Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.90; H, 4.86; N, 10.84.

Cycloaddition of 4 with Cyclohexa-1,3-diene. The residue coming from the reaction of **4** with the diene (0.4 g, 0.48 ml, 5 mmol) at 110°C for 48h was resolved into two fractions with toluene/ligroin (3:1 v/v) as eluent. The solid obtained from the first band (R_f = 0.42) was set free from the unreacted **4** (0.07 g) by sublimation at 60°C, 10 mmHg, to give (2*SR*, 6*RS*)-6-nitro-5-phenyl-3-oxa-4-azatricyclo[5.2.2.0^{2,6}]undeca-4,8-diene (**10**) (0.105 g, 62%) which was crystallized from petroleum ether as white crystals, m.p. 62-62.5°C; IR ν 1541, 1359 cm^{-1} (NO_2); ^{1}H NMR δ 1.10-1.52 (m, 3H, Hb-10 and 11-CH_2), 1.77-1.92 (m, 1H, Ha-10), 3.14-3.23 (m, 1H, H-1), 3.73-3.81 (m, 1H, H-7), 5.08 (dt, $J_{1,2}$ = 4.0 Hz, $J_{2,b10}$ = $J_{2,7}$ = 1.0 Hz, 1H, H-2), 6.27 (br t, $J_{8,9}$ = 8.2 Hz, $J_{1,9}$ = 8.0 Hz, 1H, H-9), 6.57 (ddd, $J_{8,9}$ = 8.2 Hz, $J_{7,8}$ = 6.1 Hz, $J_{1,8}$ = 0.9 Hz, 1H, H-8), 7.32-

7.48 (m, 3H, Ar-3H), 7.62-7.68 (m, 2H, Ar-2H); ^{13}C NMR δ 15.5 (t, C-10), 21.6 (t, C-11), 33.1 (d, C-7), 34.5 (d, C-1), 91.6 (d, C-2), 106.5 (s, C-6), 126.0 (d), 126.8 (s), 129.1 (d) (Ph), 130.2 (d, C-9), 130.7 (d) (Ph), 133.7 (d, C-8), 152.1 (s, C-5). Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.92; H, 5.26; N, 10.26.

The following band yielded (2*RS*, 6*SR*)-6-nitro-5-phenyl-3-oxa-4-azatricyclo[5.2.2.0^{2,6}]undeca-4,8-diene (**11**) (R_f = 0.38, 0.03 g, 18%) as ivory coloured needles, m.p. 40-41°C (from petroleum ether); IR ν 1546, 1333 cm^{-1} (NO_2); ^{1}H NMR δ 1.30-1.65 (m, 3H, 10-CH_2 and H-11), 1.80-1.92 (m, 1H, H-11), 3.18-3.28 (m, 1H, H-1), 3.90-3.98 (m, 1H, H-7), 5.38 (d, $J_{1,2}$ = 3.4 Hz, 1H, H-2), 6.08 (ddd, $J_{8,9}$ = 8.2 Hz, $J_{7,8}$ = 6.9 Hz, $J_{1,8}$ = 1.3 Hz, 1H, H-8), 6.37 (br t, $J_{8,9}$ = 8.2 Hz, $J_{1,9}$ = 8.0 Hz, 1H, H-9), 7.33-7.45 (m, 3H, Ar-3H), 7.60-7.67 (m, 2H, Ar-2H); ^{13}C NMR δ 19.1 (t, C-11), 19.3 (t, C-10), 34.5 (d, C-1 and C-7), 89.8 (d, C-2), 106.1 (s, C-6), 127.0 (s), 127.05 (d), 128.9 (d) (Ph), 129.8 (d, C-8), 130.5 (d) (Ph), 133.8 (d, C-9), 152.7 (s, C-5). Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.82; H, 5.29; N, 9.98.

(3aRS,7SR,10SR,10bSR)-11-Isopropyliden[4,10a:7,10]dimethano-6,6-dimethyl-3a-nitro-3-phenyl-3a,4,6,7,10,11-hexahydro-10bH-1-oxa-2-azacyclohept[e]indene (13). Chromatographic resolution [petroleum ether/AcOEt (15:1 v/v)] of the product obtained from the reaction of **4** with 6,6-dimethylfulvene (**12**) (0.53 g, 0.6 ml, 5 mmol) at 110°C for 48h afforded the polycyclic system **13** (R_f = 0.47, 0.246 g, 78%) that was crystallized from petroleum ether as a white solid, m.p. 124-125°C; IR ν 1547, 1355 cm^{-1} (NO_2); ^{1}H NMR δ 0.95 (s, 3H, 6-CH_3), 1.12 (s, 3H, 6-CH_3), 1.59-1.68 (AB system, J_{AB} = 11 Hz, 13-CH_2), 1.71 (s, 3H, 12-CH_3), 1.89 (s, 3H, 12-CH_3), 2.85 (d, $J_{7,8}$ = 2.5 Hz, 1H, H-7), 3.60-3.67 (m, 2H, H-4 and H-10), 5.14 (d, $J_{10b,b13}$ = 1.0 Hz, 1H, H-10b), 6.07 (br d, $J_{4,5}$ = 3.0 Hz, 1H, H-5), 6.12 (dd, $J_{8,9}$ = 6.0 Hz, $J_{9,10}$ = 2.5 Hz, 1H, H-9), 6.23 (dd, $J_{8,9}$ = 6.0 Hz, $J_{7,8}$ = 2.5 Hz, 1H, H-8), 7.32-7.48 (m, 3H, Ar-3H), 7.70-7.80 (m, 2H, Ar-2H); ^{13}C NMR δ 20.0 (q, 12-CH_3), 20.3 (q, 12-CH_3), 26.8 (q, 6-CH_3), 30.2 (q, 6-CH_3), 41.1 (s, C-6), 41.2 (d, C-10), 44.9 (t, 13-CH_2), 47.8 (d, C-4), 51.65 (d, C-7), 65.1 (s, C-10a), 95.5 (d, C-10b), 114.9 (s, C-3a), 120.7 (s, C-12), 126.4 (s), 126.5 (d), 129.0 (d) (Ph), 129.1 (d, C-5), 130.7 (d) (Ph), 135.1 (d, C-8/C-9), 136.5 (d, C-9/C-8), 138.6 (s, C-5a), 151.95 (s, C-3), 158.7 (s, C-11). Anal. Calcd. for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96. Found: C, 74.88; H, 6.70; N, 6.89.

The unreacted starting material (R_f = 0.24, 0.04 g) was recovered from the following fractions.

6-Methyl-3-phenylisoxazolo[4,5-b]pyridine (18). Chromatographic workup (toluene) of the residue obtained by treatment of **4** with 1-dimethylamino-3-methyl-1-azabuta-1,3-diene (**16**) [10] (0.34 g, 3 mmol) gave the binuclear derivative **18** (R_f = 0.31, 0.124 g, 59%) as white needles, m.p. 90-91°C (from petroleum ether); IR ν 1610, 1588 cm^{-1} (C=C, C=N); ^{1}H NMR δ 2.57 (br s, 3H, 6-CH_3), 7.49-7.60 (m, 3H, Ar-3H), 7.73 (dq, $J_{5,7}$ = 1.8 Hz, $J_{6\text{-}CH_3,7}$ = 0.8 Hz, 1H, H-7), 8.40-8.52 (m, 2H, Ar-2H), 8.62 (d, $J_{5,7}$ = 1.8 Hz, 1H, H-5); ^{13}C NMR δ 18.9 (q, 6-CH_3), 117.2 (d, C-7), 127.7 (s), 128.0 (d), 128.8 (d), 130.6 (d) (Ph), 134.3 (s, C-6), 137.7 (s, C-3a), 149.3 (d, C-5), 155.7 (s, C-3), 156.9 (s, C-7a). Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.47; H, 4.62; N, 13.05.

Reactions of 4 with 6-[(Dimethylamino)methylene]amino-1,3-dimethyluracil (19).

A. The raw product coming from the reaction of **4** with **19** [11] (0.63 g, 3 mmol) at 110°C for 48h was resolved with AcOEt/petroleum ether (3:1 v/v) as eluent; after the unreacted nitroisoxazole was recovered from the first fractions (R_f = 0.95, 0.04 g), 6-[(dimethylamino)methylene]amino-1,3-dimethyl-5-(3-phenylisoxazol-5-yl)uracil (**22**) (R_f = 0.39, 0.056 g, 20%) was isolated as a pale yellow solid, m.p. 176-177°C (from ether); IR ν 1700, 1637 cm^{-1} (CO); ^{1}H NMR δ 3.0 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3),3.41 (s, 3H, 3-CH_3), 3.46 (s, 3H, 1-CH_3), 7.06 (s, 1H, H-10), 7.33 (s, 1H, H-8), 7.40-7.48 (m, 3H, Ar-3H), 7.78-7.86 (m, 2H, Ar-2H); ^{13}C NMR δ 28.2 (q, 3-CH_3), 30.8 (q, 1-CH_3), 34.7 (q, NCH_3), 40.6 (q, NCH_3), 88.4 (s, C-5), 102.0 (d, C-10), 126.6 (d), 128.7 (d), 129.0 (s), 129.7 (d) (Ph), 151.2 (s, 2-CO), 155.6 (d, C-8), 158.8 (s, C-6), 160.9 (s, 4-CO), 162.2 (s, C-11), 165.8 (s, C-9). Anal. Calcd. for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 61.29; H, 5.32; N, 20.08.

B. The reaction mixture obtained from the same reagents at 70°C for 6 days was treated as above to give, in order of decreasing mobility, the starting nitro compound **4** (0.126 g) and 6-[(dimethylamino)methylene]amino-1,3-dimethyl-5-(4-nitro-3-phenyl-4,5-dihydroisoxazol-5-yl)uracil (**21**) (R_f = 0.48, 0.053 g, 39%) that was crystallized from AcOEt as white needles, m.p. 166-167°C; IR ν 1693, 1644 (CO), 1561, 1375 cm^{-1} (NO_2); ^{1}H NMR δ 2.99 (s, 3H, NCH_3), 3.10 (s, 3H, NCH_3), 3.31 (s, 3H, 3-CH_3), 3.37 (s, 3H, 1-CH_3), 5.77 (d, $J_{9,10}$ = 5.5 Hz, 1H, H-10), 6.86 (d, $J_{9,10}$ = 5.5 Hz, 1H, H-9), 7.38-7.45 (m, 3H, Ar-3H), 7.50 (s, 1H, H-8), 7.72-7.78 (m, 2H, Ar-2H); ^{13}C NMR δ 28.0 (q, 3-CH_3), 30.9 (q, 1-CH_3), 34.5 (q, NCH_3), 40.6 (q, NCH_3), 83.9 (d, C-10), 94.0 (d, C-9), 94.2 (s, C-5), 126.6 (d), 127.0 (s), 129.0 (d), 130.6 (d) (Ph), 151.4 (s, 2-CO), 151.8 (s, C-11), 154.7 (d, C-8), 161.0 (s, C-6), 162.3 (s, 4-CO). Anal. Calcd. for $C_{18}H_{20}N_6O_5$: C, 54.00; H, 5.03; N, 20.99. Found: C, 54.22; H, 5.01; N, 20.75.

The isoxazole **22** (0.025 g, 21%), identical with the material obtained as above, was isolated from the following fractions.

Conversion of Compound 21 into 22. A solution of **21** (0.1 g, 0.25 mmol) in $CHCl_3$ (1 ml) was heated in a sealed tube at 110°C for 3 days; chromatographic resolution of the residue left by removal of the solvent afforded a small amount of the starting material (0.015 g) and compound **22** (0.053 g, 71%), identical with the product described above.

X-Ray Structural Analysis of 22.[12] Compound **22**: $C_{18}H_{19}N_5O_3$, M = 353.38, triclinic, space group $P\bar{1}$, a = 7.676(7), b = 10.581(4), c = 11.522(3) Å, α = 73.24(3), β = 77.63(6), γ = 79.94(6)°, V = 868.9(9) Å^3, Z = 2, $F(000)$ = 372, μ = 0.10 mm^{-1}, D_c = 1.35 g cm^{-3}, graphite monochromated (Mo-Kα) radiation (λ = 0.71069Å).

3204 Reflections ($2\theta_{max}$ = 50°) were collected on an Enraf-Nonius CAD4 automatic diffractometer. Intensity data were corrected for Lorentz and polarization effects and an absorption correction was applied by using the Walker and Stuart method.[13] The crystal structure was solved by direct methods of SIR 92,[14] and refined using the full-matrix least squares on F^2 provided by SHELXL-93.[15] 2489 Reflections having $I > 2\sigma(I)$ were used in the refinement of 240 parameters reaching a final R factor of 0.055. All the non hydrogen atoms were refined anisotropically, while for the hydrogen ones, which were introduced in calculated positions and refined according to their linked atoms, an overal isotropic temperature factor was used and refined to 0.095 Å^2.

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