Tetrahedron Vol. 45, No. 18, pp. 5917 to 5924, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

REARRANGEMENT OF ISOXAZOLINE-5-SPIRO DERIVATIVES. PART 4.[1] SYNTHESIS OF MEDIUM SIZE BENZOFUSED AZAHETEROCYCLES

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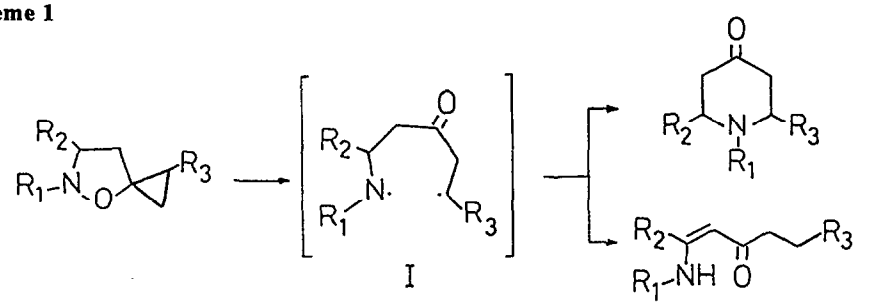
(*Received in UK* 1 *June* 1989)

Abstract - Medium sized aza-heterocycles are obtained by sequential cycloaddition-rearrangement of C,N-diphenylnitrone (**1**) to methylenecyclopropane (**2**) or methylenecyclobutane (**8**) besides the common rearrangement products (mainly the pyridone **5** and the azepinone **10**). Thus, the valuable 2,3,5,6-tetrahydro- 2-phenyl-1-benzazocin-4(1*H*)-one (**6**) and 1,2,3,5,6,7-hexahydro-2-phenyl-4*H*-1- benzazonin-4-one (**11**) are produced straightforwardly in 14% and 12% yields respectively. Delocalization of the diradical intermediate on the N-aryl ring is responsible for the radical coupling on the *ortho* carbon atom of the aromatic ring.

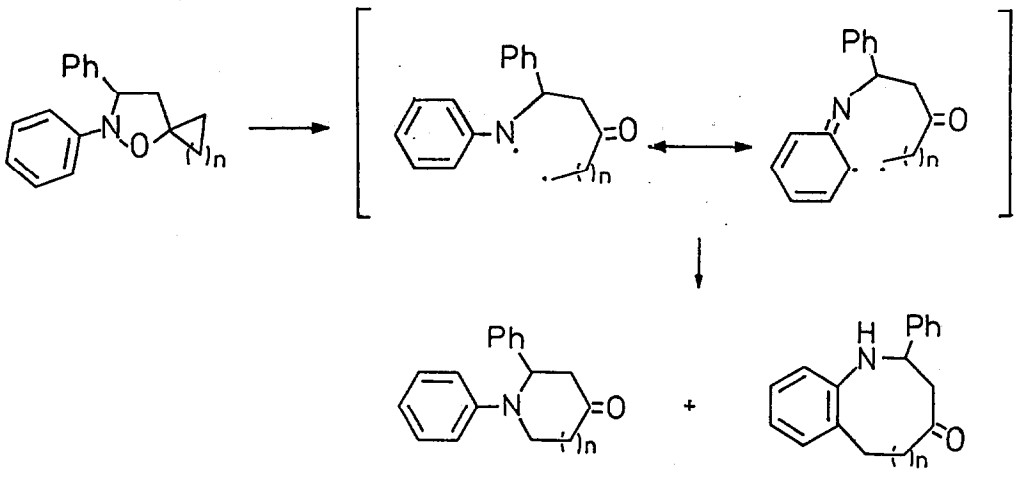
The thermal rearrangement of 5-spirocyclopropaneisoxazolidines (Scheme 1) has been demonstrated to be a very convenient route for the synthesis of selectively substituted tetrahydropyrid-4-ones (Scheme 1).[2] The availability of precursor isoxazolidines from 1,3-dipolar cycloaddition of nitrones to methylenecyclopropanes substantiates the general application of this process. Particularly, cyclic nitrones gave N-bridgehead bicyclic ketones, attractive targets as precursors of natural alkaloids.[2b] The same process was then extended to the homologous spirocyclobutane derivatives.[3]

Scheme 1



In the course of our study aiming at the disclosure of other useful synthetic applications of the rearrangement of spiroisoxazolidines, we considered the effects of substituents on the diradical intermediate I.[2b,4] In principle, aromatic substituents on the nitrogen in I should delocalize the radical and possibly lead to different, benzo-annulated rearrangement products (Scheme 2).

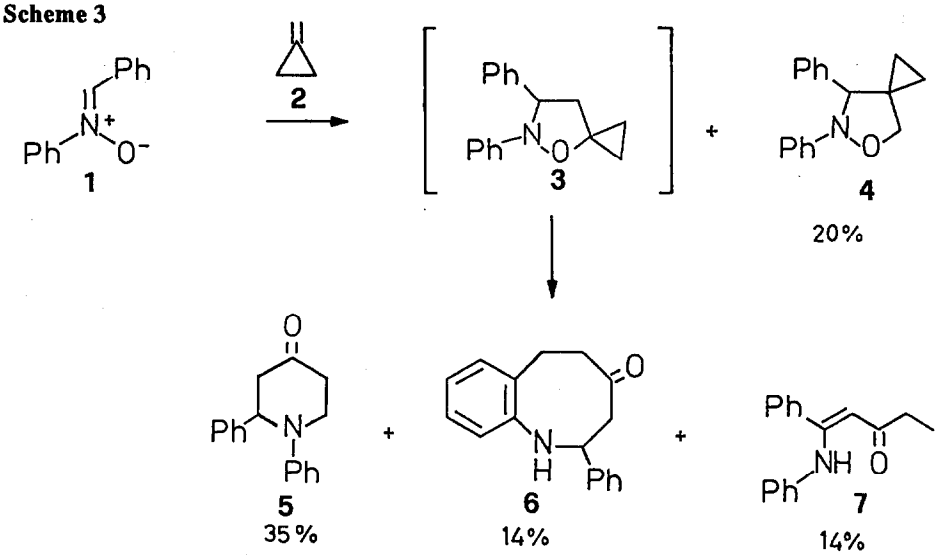
Scheme 2



Results and discussion

A mixture of C,N-diphenylnitrone (1) and methylenecyclopropane (2) in benzene afforded, upon heating, a complex mixture of the compounds 4-7 (Scheme 3).

Scheme 3

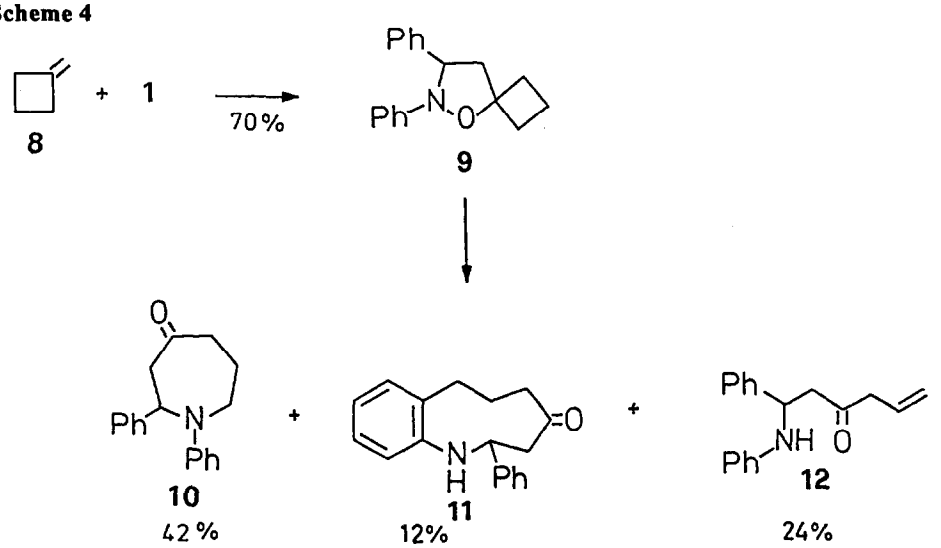


The 4-spiroregioisomer **4**, produced in the cycloaddition,[2] does not undergo any rearrangement in these conditions and can be recovered in 20% yield. The 5-spiroisoxazolidine **3** cannot be isolated, because the rearrangement occurs smoothly giving products **5**, **6** and **7** in 35%, 14% and 14% yield respectively, with respect to the starting nitrone. The assignment of the structure to compounds **5** and **6** has been easily made by means of NMR spectroscopy (see experimental section). The broad signal at δ 3.28 in the ^{1}H NMR spectrum, disappearing by treatment with D_2O, is diagnostic for the proton on nitrogen in **6**. The ^{13}C NMR spectrum of **6**, moreover, shows three quaternary aromatic carbon signals at 145.53, 144.03 and 136.27 ppm attesting the presence of a fused aromatic ring.

The mixture composition does not change if the reaction is carried out at lower temperature. Even at room temperature the rearrangement products can be observed with almost the same ratio, thus demonstrating that the rearrangement is much easier for N-aryl than for N-alkyl compounds. This is probably due to the weakening of the N-O bond[5] and to the stabilization of the transition state by delocalization of the incipient radical on the aryl ring. Anyway, at room temperature the cycloaddition and the rearrangement proceed much more slowly and are less convenient. In these conditions also the 5-spirocyclopropane regioisomer **3** can be detected.[6]

Relying on the results obtained in the rearrangement of the homologous 5-spirocyclobutaneisoxazolidines,[3] we extended the application of this process. As expected,[3] the isoxazolidine **9** was isolated as the sole regioisomer by cycloaddition of **1** and methylenecyclobutane (**8**) (Scheme 4). Subjected to FVT conditions (500°C, 0.02 mmHg),[3] **9** gave compounds **10**, **11** and **12** in 42%, 12% and 24% isolated yield, respectively (Scheme 4).

Scheme 4



Assignment of the azepinone structure to **10** and the azoninone structure to **11** followed as previously (see experimental section). Compound **12** was assigned the structure of unconjugated unsaturated ketone on the basis of the frequencies of the C=O in the ^{13}C NMR and IR spectra and of the presence of a terminal vinyl group, evidenced in the ^{1}H NMR spectrum.

Thus, the N-aryl substitution is responsible for the formation of the benzazocine **6** and the benzazonine **11** through the delocalized diradical intermediate. No product of this type, in fact, was observed with N-alkyl substituted nitrones.[2] An analogous behaviour of N-aryl substituted isoxazolidines has been observed in related thermal rearrangements.[7]

The new synthesis of the shown medium sized aza-heterocycles appears to be very useful and convenient. Despite the low yield, these valuable heterocycles originate straightforward from readily accessible starting materials, and their synthesis requires only one careful separation by flash column chromatography. Only a limited number of synthetic methods of these ring systems are reported in the literature and mostly refer to lactams.[8] Very recent syntheses appeared in the literature during the preparation of this manuscript.[9] Moreover, benzazocinones have been recognized as key precursors for the synthesis of potent antitumor antibiotics of the mitosane class.[10]

Experimental section

Methylenecyclopropane (**2**) and methylenecyclobutane (**8**) were purchased from Fluka and Aldrich respectively and were used without any further purification. The pyrolysis oven used in the flash vacuum thermolysis (FVT) experiment 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 R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}) obtained using the same eluant as in the column chromatographies. Melting points were observed with a microscope RCH Kofler apparatus. NMR spectra ($CDCl_3$ as solvent) were recorded on Varian XL 300 (^{1}H, 300 MHz) and Varian FT-80A (^{13}C, 20 MHz) spectrometers; chemical shift values are reported in ppm from tetramethylsilane: notations s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. IR spectra (in CCl_4 solution, unless otherwise stated) were recorded on a Perkin-Elmer 881 spectrophotometer. Mass spectra were recorded at 70 eV by GC inlet on a 5790A-5970A Hewlett-Packard instrument. Combustion analyses were carried out with a Perkin-Elmer 240 C elemental analyzer.

Reaction of C,N-Diphenylnitrone (1) with Methylenecyclopropane (2): 6,7-Diphenyl-5-oxa-6-azaspiro[2.4]heptane (4), 1,2-Diphenylpiperidin-4-one (5), 2,3,5,6-Tetrahydro-2-phenyl-1-benzazocin-4(1*H*)-one (6) and 1-(Phenylamino)-1-phenylpent-1-en-3-one (7). C,N-diphenylnitrone (1, 394 mg, 2 mmol) was dissolved in 1 mL of dry benzene and reacted with an excess methylenecyclopropane (2) in a sealed tube at 60°C for 1 day. The crude reaction mixture was then concentrated and fractionated by flash-chromatography on silica gel (eluant petroleum ether-dichloromethane 3:2). Compounds 4 (R_f 0.41, 99 mg, 20% yield) and 7 (R_f 0.31, 71 mg, 14% yield) were thus collected. Then, 248 mg of a 2.5:1 mixture (calculated by ^{1}H-NMR) of 5 and 6, corresponding to 35% and 14% yields respectively, were collected by eluting with dichloromethane-petroleum ether 4:1. Compounds 5 and 6 can be separated by a further flash column chromatography with the same eluant with R_f 0.39 and 0.36 respectively.

4: white crystals, mp 69-69.5°C. ^{1}H NMR δ 7.45-7.15 (m, 7 H), 7.05-6.85 (m, 3 H), 4.41 (s, 1 H), 4.09 and 4.06 (AB system, J = 7.7 Hz, 2 H), 0.76 (ddd, J = 9.9, 6.2, 5.0 Hz, 1 H), 0.65 (ddd, J = 9.7, 6.3, 5.0 Hz, 1 H), 0.55 (ddd, J = 9.9, 6.3, 5.2 Hz, 1 H), 0.22 (ddd, J = 9.7, 6.2, 5.2 Hz, 1 H); ^{13}C NMR δ 151.60 (s), 139.47 (s), 128.50 (d, 4 C), 127.51 (d), 127.34 (d, 2 C), 121.63 (d), 115.00 (d, 2 C), 75.27 (d), 73.96 (t), 32.35 (s), 9.06 (t), 8.59 (t); IR ($CDCl_3$) 1600, 1488, 1264 cm^{-1}; MS m/z (relative intensity) 251 (41, M^+), 250 (11), 182 (100). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.92; H, 6.77; N, 5.42%.

5: yellow oil. ^{1}H NMR δ 7.40-7.20 (m, 7 H), 6.90-6.80 (m, 3 H), 5.17 (t, J = 5.3 Hz, 1 H), 3.82-3.73 (m, 1 H), 3.67-3.58 (m, 1 H), 2.99 (d, J = 5.3 Hz, 2 H), 2.60 (m, 2 H); ^{13}C NMR δ 207.90 (s), 149.09 (s), 141.36 (s), 129.19 (d, 2 C), 128.60 (d, 2 C), 127.23 (d), 126.46 (d, 2 C), 118.92 (d), 114.97 (d, 2 C), 59.59 (d), 45.57 (t), 43.40 (t), 39.78 (t); IR 1723 cm^{-1}; MS m/z (relative intensity) 251 (100, M^+), 208 (15), 181 (25), 180 (33), 105 (63), 104 (64), 77 (60). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.02; H, 7.11; N, 5.64%.

6: crystals, mp 126-127°C. ^{1}H NMR δ 7.45-7.05 (m, 8 H), 6.90-6.80 (m, 1 H), 4.13 (dd, J = 10.5, 2.4 Hz, 1 H), 3.83-3.70 (m, 1 H), 3.28 (br, 1 H), 3.23 (t, J = 11.1 Hz, 1 H), 2.94-2.83 (m, 2 H), 2.62-2.50 (m, 1 H), 2.40 (dd, J = 11.5, 2.4 Hz, 1 H); ^{13}C NMR δ 210.92 (s), 145.53 (s), 144.03 (s), 136.27 (s), 129.93 (d), 128.79 (d, 2 C), 127.75 (d, 2 C), 126.37 (d, 2 C), 126.03 (d), 125.23 (d), 63.37 (d), 49.78 (t), 48.60 (t), 26.46 (t); IR 3345 (br), 1710 cm^{-1}. The product decomposed on GC inlet at 250°C in the GC-MS apparatus.[11] Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.02; H, 6.89; N, 5.95%.

7: yellow oil. ^{1}H NMR δ 12.27 (br, 1 H), 7.40-7.20 (m, 5 H), 7.07 (m, 2 H), 6.92 (m, 1 H), 6.69 (m, 2 H), 5.37 (s, 1 H), 2.45 (q, J = 7.5 Hz, 2 H), 1.16 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 200.97 (s), 159.37 (s), 144.71 (s), 130.75 (s), 129.37 (d), 128.73 (d, 2 C), 128.51 (d, 2 C), 128.32 (d, 2 C), 123.57 (d), 122.77 (d, 2 C), 99.53 (d), 35.59 (t), 9.48 (q); IR 3200 (br), 1612, 1594, 1569 cm^{-1}; MS m/z (relative intensity) 251 (13, M^+), 222 (100), 194 (22).

6,7-Diphenyl-5-oxa-6-azaspiro[3.4]octane (9). A mixture of C,N-diphenylnitrone (**1**, 470 mg, 2.40 mmol) and methylenecyclobutane (**8**, 90 mg, 1.32 mmol) in 0.7 mL of dry benzene was heated at 100°C in a sealed tube for 12 h. After removal of the solvent, the resulting mixture was purified by flash column chromatography (eluant dichloromethane-petroleum ether 2:1). Pure **9** (R_f 0.39, 245 mg, 70% yield) which crystallized as a white solid on standing for several days, was obtained. Recrystallized from *n*-hexane, mp 46-48°C. ^{1}H NMR δ 7.53 (m, 2 H), 7.40 (m, 2 H), 7.32 (m, 1 H), 7.22 (m, 2 H), 7.01 (m, 2 H), 6.93 (m, 1 H), 4.66 (t, J = 7.6 Hz, 1 H), 2.82 (dd, J = 11.9, 7.4 Hz, 1 H), 2.58-2.38 (m, 2 H), 2.46 (dd, J = 11.9, 7.8 Hz, 1 H), 2.16-2.02 (m, 2 H), 1.89-1.77 (m, 1 H), 1.69-1.54 (m, 1 H); ^{13}C NMR δ 152.46 (s), 141.92 (s), 128.59 (d, 2 C), 128.37 (d, 2 C), 127.17 (d), 126.30 (d, 2 C), 121.12 (d), 114.64 (d, 2 C), 83.04 (s), 69.66 (d), 49.64 (t), 35.90 (t), 33.70 (t), 12.63 (t); IR (neat) 1599, 1487, 1255 cm^{-1}; MS m/z (relative intensity) 265 (18, M^+), 222 (21), 195 (10), 194 (23), 182 (100), 181 (24), 180 (40), 104 (60), 91 (40), 77 (74), 51 (31), 41 (41). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.32; H, 7.24; N, 5.00%.

Thermal Rearrangement of 9: Hexahydro-1,2-diphenyl-4*H*-azepin-4-one (10), 1,2,3,5,6,7-Hexahydro-2-phenyl-4*H*-1-benzazonin-4-one (11) and 1-(Phenylamino)-1-phenylhex-5-en-3-one (12). The spiroisoxazolidine **9** (850 mg, 3.2 mmol) was subjected to FVT (T 500°C, P 0.02 mmHg) by vaporization at 175°C. The collected crude mixture (820 mg), by fractionation by flash column chromatography (eluant dichloromethane-petroleum ether 4:1), afforded the products **12** (R_f 0.34, 204 mg, 24% yield), **10** (R_f 0.27, 408 mg, 42% yield)[12] and **11** (R_f 0.19, 100 mg, 12% yield).

10: white crystals, mp 93-94°C (*n*-hexane). ^{1}H NMR δ 7.36-7.20 (m, 5 H), 7.14 (m, 2 H), 6.68 (m, 1 H), 6.61 (m, 2 H), 4.94 (dd, J = 11.5, 6.1 Hz, 1 H), 4.04 (dt, J = 15.9, 3.7 Hz, 1 H), 3.87 (ddd, J = 15.9, 11.0, 2.7 Hz, 1 H), 3.14 (dd, J = 12.9, 11.5 Hz, 1 H), 2.98 (ddd, J = 12.9, 6.1, 1.2 Hz, 1 H), 2.62-2.46 (m, 2 H), 2.10-1.90 (m, 2 H); ^{13}C NMR δ 209.25 (s), 147.92 (s), 141.36 (s), 129.13 (d, 2 C), 128.88 (d, 2 C), 127.04 (d), 125.60 (d, 2 C), 116.79 (d), 111.96 (d, 2 C), 57.52 (d), 49.99 (t), 44.35 (t), 42.83 (t), 23.20 (t); IR 1714, 1597, 1502 cm^{-1}; MS m/z (relative intensity) 265 (22, M^+), 222 (11), 194 (17), 181 (14), 180 (16), 161 (10), 146 (13), 119 (22), 106 (100), 105 (24), 104 (56), 77 (69). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.48; H, 7.12; N, 5.20%.

11: white crystals, mp 117-118°C (*n*-hexane). ^{1}H NMR δ 7.47 (m, 2 H), 7.39 (m, 2 H), 7.31 (m, 1 H), 7.07 (m, 2 H), 6.92 (m, 1 H), 6.74 (m, 1 H), 4.71 (dd, J = 11.5, 5.9 Hz, 1 H), 3.04 (br, 1 H), 3.02 (dd, J = 15.0, 5.9 Hz, 1 H), 2.79 (ddd, ^{13} J = 14.4, 11.7, 4.0 Hz, 1 H), 2.78 (dd, J = 15.0, 11.5 Hz, 1 H), 2.65 (ddd, J = 15.0, 12.1, 3.4 Hz, 1 H), 2.57 (dt, J = 14.4, 4.5 Hz, 1 H), 2.37 (ddq, J = 13.5, 12.1, 4.1 Hz, 1 H), 2.12 (ddd, J = 15.0, 5.3, 3.9 Hz, 1 H), 1.66 (m, 1 H); ^{13}C NMR δ 211.46 (s), 148.26 (s), 144.56 (s), 131.88 (s), 129.94 (d), 128.61 (d, 2 C), 127.63 (d), 127.04 (d), 125.92 (d, 2 C), 122.80 (d), 121.34 (d), 62.33 (d), 52.72 (t), 36.91 (t), 28.66 (t), 25.91 (t); IR 3416,

3320 (br), 1707 cm^{-1}; MS[14] m/z (relative intensity) 265 (8, M^+), 222 (13), 208 (17), 207 (62), 206 (100), 195 (21), 194 (30), 193 (14), 130 (33), 91 (46), 43 (28). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.32; H, 7.43; N, 5.16%.

12: white solid, mp 88.5-89.5°C. ^1H NMR δ 7.39-7.19 (m, 5 H), 7.08 (m, 2 H), 6.65 (m, 1 H), 6.53 (m, 2 H), 5.80 (ddt, J = 17.1, 10.2, 6.9 Hz, 1 H), 5.15 (dq, J = 10.2, 1.3 Hz, 1 H), 5.05 (dq, J = 17.1, 1.5 Hz, 1 H), 4.83 (t, J = 6.3 Hz, 1 H), 4.47 (br, 1 H), 3.07 (d, J = 6.9 Hz, 2 H), 2.92 (d, J = 6.3 Hz, 2 H); ^{13}C NMR δ 206.77 (s), 146.61 (s), 142.29 (s), 129.71 (d), 128.96 (d, 2 C), 128.62 (d, 2 C), 127.21 (d), 126.11 (d, 2 C), 119.17 (t), 117.67 (d), 113.60 (d, 2 C), 54.19 (d), 49.50 (t), 48.28 (t); IR 3418 (br), 1714, 1603, 1501 cm^{-1}; MS[15] m/z (relative intensity) 265 (11, M^+), 182 (100), 181 (11), 180 (12), 104 (22), 93 (14), 77 (27), 41 (24). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.37; H, 7.31; N, 5.29%. Compound **12** is contaminated (ca. 10%) by its conjugated isomer (*Z*)-1-(phenylamino)-1-phenylhex-4-en-3-one: ^1H NMR δ 6.18 (dq, J = 11.4, 6.9 Hz, 1 H), 6.10 (dq, J = 11.4, 1.3 Hz, 1 H), 2.06 (dd, J = 6.9, 1.3 Hz, 3 H); ^{13}C NMR δ 199.32 (s), 144.24 (d), 54.50 (d), 51.58 (t), 15.84 (q); MS m/z (relative intensity) 265 (23, M^+), 250 (21), 188 (12), 181 (17), 180 (33), 146 (19), 131 (93), 120 (72), 119 (58), 118 (24), 104 (100), 103 (22), 77 (86), 51 (31).

Acknowledgment. Ministero della Pubblica Istruzione - Italy (MPI 60% and 40%) and C.N.R. are gratefully acknowledged for financial support.

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11. Two main peaks were detected by GC-MS, which possibly arise by loss of water, and water and hydrogen respectively from product **6**. Their mass spectra are: m/z (relative intensity) 233 (90, **6**-H_2O^+), 232 (100), 217 (18), 156 (66), 129 (31), 128 (24) and 231 (44, **6**-H_2O-H_2+), 230 (100), 114 (11).

12. Some of the collected fractions contained 1-(phenylamino)-1-phenylhex-1-en-3-one (6% calculated yield). ^{1}H NMR δ 12.33 (br, 1 H), 7.40-6.60 (m, 10 H), 5.39 (s, 1 H), 2.42 (t, J = 7.4 Hz, 2 H), 1.69 (sextet, J = 7.4 Hz, 2 H), 0.97 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 200.38 (s), 159.26 (s), 100.08 (d), 44.71 (t), 19.03 (t), 13.93 (q); MS m/z (relative intensity) 265 (10, M^+), 222 (100), 194 (22), 77 (26).

13. Mostly hindered by the peak at 2.78 ppm (dd). The coupling constants were established by irradiation at 4.71 ppm, which caused the proton at 2.78 ppm to collapse into a doublet.

14. Also compound **11** partially decomposes on GC inlet (250°C) giving a product which has lost a molecule of water [MS m/z (relative intensity) 247 (45, **11**-H_2O^+), 246 (100), 219 (12), 218 (54), 217 (30)].

15. Compound **12** partially decomposes on GC inlet (250°C) to benzylideneaniline. Long elution times in the GC column cause its complete isomerization to the conjugated ketones, *E* and *Z*, which give almost superimposable mass spectra.