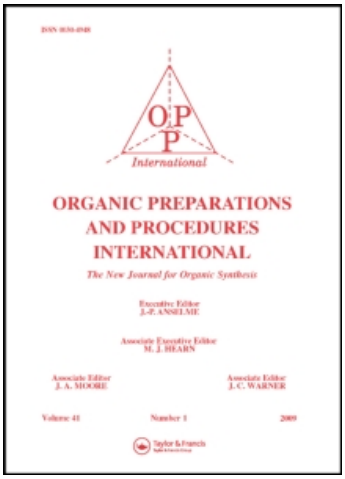

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SYNTHESIS OF 2,6-DIPHENYL-9-METHYLENE-1-AZA-7-OXASPIRO[4.5]DECAN-8-ONES

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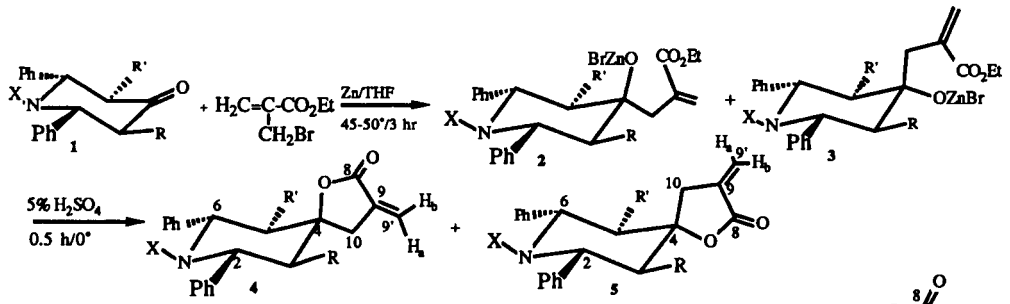
The occurence of the α-methylene-γ-butyrolactone moiety in nearly 10% of all structurally elucidated natural products[1] and the diverse biological activity exhibited by compounds containing an α-methylene-γ-butyrolactone system[2] have attracted the attention of a large number of workers and prompted several reviews.[3] With a view to exploit their carcinostatic properties, a few carbocyclic[4] and some heterocyclic[5] spiro α-methylene-γ-butyrolactone systems have been synthesized starting from 2,6-diphenylpiperidin-4-ones. On the assumption that the incorporation of a heterocyclic group would enhance the hydrophilic character of these compounds, and thus enable them to



(a) X = H, R = R' = CH_3 (b) X = R = R' = CH_3

(c) X = R' = H, R = CH_3 (d) X = R = CH_3, R' = H

(e) X = R' = H, R = i-Pr (f) X = CH_3, R = i-Pr, R' = H

be asborbed more easily, we report the preparation of 9-methylene-1-aza-7-oxaspiro[4.5]decan-8-ones (Table 1). The synthesis of the spirolactones, via a Reformatsky-type reaction, is outlined as shown. The appropriate piperidin-4-one **1** was allowed to react with activated zinc[6] and ethyl α-

(bromomethyl)acrylate.[7] It is imperative that this ester be freshly distilled to give the highest yields of the final lactone. When complete, the reaction mixture is treated with cold 5% sulfuric acid. Although there exists the possibility of formation of both spirolactones **4** and **5**, only one white

TABLE 1. IR and Physical Data for 9-Methylene-1-aza-7-oxaspiro{4.5}decan-8-ones

			IR(KBr),cm^{-1}			Solvent of
Compd	yield (%)	mp,°C	C=O stretch	C=C stretch	N-H stretch	Crystallization
4a	75	136-137	1750	1670	3330	benzene
4b	55	271-272	1760	1660		benzene
4c	45	119-120	1770	1670	3320	methanol
4d	72	199-200	1770	1670		benzene
4e	72	126-127	1760	1670	3300	pet. ether
4f	54	207-208	1760	1670		benzene

solid, with a sharp melting point, was isolated in each case. Considering that the steric requirements of the OZnBr group are less than that of the CH_2-C(=CH_2)$CO_2C_2H_5$ group (thus favoring intermediate **2** over **3**) and the fact that the single crystal X-ray analysis of similar lactones has established the existence of an axial C-O bond,[4,5] we tentatively conclude that the lactones produced have configuration **4** and arise from **2**. This conclusion is corroborated by the spectral analysis of the lactones.

The ^{1}H NMR spectral data for the spirolactones are reported in Table 2. The signal for H(2) appears as a doublet for *all* systems studied. The observed coupling constants, $^3J_{H(2),H(2)}$ = 10.2-11.1 Hz, are typical of the vicinal coupling constant $^3J_{trans}$ for the diaxial protons in the chair conformation of a cyclohexane-like system.[8] Because a symmetry plane is present, H(2) and H(6) in compounds **4a** and **4b** are magnetically equivalent. However, the signals for H(6) in the other systems appear as a doublet of doublets with coupling constants of $^3J_{H(6a),H(5a)}$ = 9.4-11.5 Hz and $^3J_{H(6a),H(5e)}$ = 2.5-5.5 Hz, typical of the $^3J_{trans}$ and $^3J_{cis}$, respectively, in the chair conformation of a simple cyclohexyl system.[8] The above observations strongly support the existence of the six-membered ring in the chair conformation, with the C(2)-H and C(6)-H bonds in the axial positions and the C(3)-alkyl and C(5)-alkyl bonds in the equatorial positions. Comparison of the chemical shifts for H(2) and H(6) in the N-CH_3 systems (**4b**, **4d**, and **4f**) with those for the corresponding protons in the related systems (**4a**, **4c**, and **4e**) reveals the electron-releasing (and

TABLE 2. ^{1}H NMR Data for 9-Methylene-1-aza-oxaspiro{4.5}decan-8-ones[a,b]

Compd	H(2)	H(3)	H(5)	H(6)	NH/NMe	H_a(9')	H_b(9')	H(10)	H'(10)	Other
4a	3.88(d, J= 10.2 Hz)	1.97(dq, J= 10.2, 6.8 Hz)[c]	same as H(3)	same as H(2)	1.88(bs)	5.61[d]	6.25[e]	2.88[f]	same as H(10)	0.65 (d, 3 H, CH_3, J=6.7 Hz), 7.22-7.40 (m, 10 H, Ar-H)
4b	3.23 (d, J= 10.5 Hz)	2.03 (dq, J= 10.4, 6.6 Hz)[c]	same as H(3)	same as H(2)	1.61 (s)	5.61[d]	6.25[e]	2.85[f]	same as H(10)	0.55 (d, 3 H, CH_3, J=6.6 Hz) 7.23-7.30 (m, 10 H, Ar-H)
4c	3.90 (d, J= 10.2 Hz)		2.06 (dd, J= 11.5, 2.8 Hz)[g]	4.28 (dd, J= 11.5, 2.5 Hz)		5.61[h]	6.25[i]	2.63 (dt J=17.7, 2.7 Hz)[j]	2.98 (dt J=17.7, 2.7 Hz)[k]	0.63 (d, 3 H, CH_3, J=6.7 Hz), 1.84, 1.96 [m, 3 H, NH, H(3), H(5)] eq, 7.21-7.42 (m, 10 H, Ar-H)
4d	3.24 (d, J=10.4 Hz)	1.96 (dq, J= 10.5, 6.8 Hz)	2.02-2.05 (m)	3.63 (dd, J= 9.4, 5.5 Hz)	1.72 (s)	5.59[h]	6.24[i]	2.58 (dt J=17.7, 2.7 Hz)[j]	2.93 (dt J=17.7, 2.7 Hz)[k]	0.58 (d, 3 H, CH_3, J=6.7 Hz) 7.22-7.41 (m, 10 H, Ar-H)
4e	4.23 (d, J=10.8 Hz)	←1.87-2.03 (m)→		4.24 (dd, J=10.9, 2.9 Hz)	1.73 (bs)	5.62[h]	6.27[i]	2.65 (dt, J=18.1, 2.7 Hz)	3.08 (dt, J=18.1, 2.7 Hz)	0.45 (d, 3 H, CH_3 of *i*-Pr, J=7.2 Hz), 0.98 (d, 3 H, CH_3 of *i*-Pr, J=7.2 Hz), 1.80 (h, 1 H, CH of *i*-Pr, J=7.2 Hz), 7.19-7.48 (m, 10 H, Ar-H)
4f	3.50 (d, J=11.1 Hz)	←1.92-2.11 (m)→		3.62 (dd, J=11.5, 2.7 Hz)	1.66 (s)	5.60[h]	6.26[i]	2.59 (dt, J=18.0, 2.7 Hz)[j]	3.05 (dt, J=18.0, 2.7 Hz)[k]	0.28 (d, 3 H, CH_3 of *i*-Pr, J=7.3 Hz), 1.02 (d, 3 H, CH_3 of *i*-Pr, J=7.3 Hz), 1.80 (h, 1 H, CH of *i*-Pr, J=7.3 Hz), 7.21-7.47 (m, 10 H, Ar-H)

[a] In parts per million downfield from Me_4Si in $DCCl_3$. [b] Abbreviations used; s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; h, heptets; bs, broad singlet; m, multiplet. [c] The signal pattern appeared as two slightly displaced quartets. [d] "M" portion of AMX_2 pattern where $J_{AM}<J_{MX}$=2.7 Hz. The center of the triplet is taken as the peak position. [e] "A" portion of AMX_2 pattern where $J_{AM}<J_{AX}$=2.7 Hz. The center of the triplet is taken as the peak position. [f] Three-line pattern resulting from X_2 of AMX_2 where $J_{AX}\approx J_{MX}$=2.7 Hz. [g] Signal for the axial proton. [h] "M" portion of AMXX' pattern where $J_{AM}<J_{MX}\approx J_{AX'}$=2.7 Hz. The Center of the triplet is taken as the peak position. [i] "A" portion of AMXX' pattern where $J_{AM}<J_{AX}\approx J_{AX'}$=2.7 Hz. The center of the triplet is taken as the peak position. [j] "X" portion of AMXX' where $J_{XX'}>J_{AX}=J_{MX}$= 2.7 Hz. [k] "X" portion of AMXX' WHERE $J_{XX'}>J_{AX'}=J_{MX'}$=2.7 Hz.

hence shielding) effect of the N-CH_3 group on the neighboring proton signals (Table 3). The assignments of the signals at δ 5.61 and δ 6.25 for $H_a(9')$ and $H_b(9')$, respectively, were made on

TABLE 3. ^1H NMR Chemical Shift Differences for H(2) and H(6) signals in the N-H and N-CH_3 Systems

Compd	H(2)	H(6)
δ(4b)-δ(4a)	-0.65	
δ(4d)-δ(4c)	-0.66	-0.65
δ(4f)-δ(4e)	-0.73	-0.62

the basis of the empirical correlation [$\delta = 5.28 + Z_{gem} + Z_{trans}$] developed by Tobey[9] and Pascual, Meier, and Simon[10] for the chemical shift of a proton on a double bond. The two H(10) protons in systems **4c-4f** and the two methyl groups of C(3)-$CH(CH_3)_2$ in systems **4e** and **4f** are diastereomeric and appear at different frequencies (Table 2).

The ^{13}C NMR spectral data for substituted 9-methylene-1-aza-7-oxaspiro[4.5]decan-8-ones are recorded in Table 4. Also included in Table 4 are the ^{13}C NMR data of 2,6-diphenyl-3,5-dimethyl-9-methylene-1,7-dioxaspiro[4.5]decan-8-one (**6**) for comparison purposes.[11] Wherever ambiguity occurred in identifying signals, assignments were made on the basis of signal multiplicity observed in the off-resonance spectra. The effect of the heteroatom at the 1-position on the electron density around C(2) and C(6) atoms can be gauged from a comparison of the chemical shift values for these carbons in compounds **4a** (NH), **4b** (NCH_3), and **6** (O). Such shifts reveal a heteroatom deshielding effect in the order O>NCH_3>NH. A similar observation has been reported in the case of 1-hetera-2,6-diphenyl-4-cyclohexanones.[12] In summary, we have obtained the first examples of the family of 9-methylene-1-aza-7-oxaspiro[4.5]decan-8-ones starting from 2,6-diphenylpiperidin-4-ones using a Reformatsky reaction. Ring closure of the presumed intermediate tertiary alcohol was effected with cold 5% sulfuric acid and gave, after recrystallization, highly crystalline, spirolactones. Biological data will be reported elsewhere.

EXPERIMENTAL SECTION

Melting points were obtained on a Toshniwal melting point apparatus and are uncorrected.The ^1H NMR spectra and the broad band and off-resonance, proton-decoupled ^{13}C NMR spectra were recorded on a Varian XL-300 NMR spectrometer operating at 299.99 MHz for ^1H and at 75.4 MHz for ^{13}C resonances with tetramethylsilane as the internal standard. The IR specrta were collected on a Beckmann IR-5a unit.

TABLE 4 ^{13}C NMR Data for 9-Methylene-1-aza-7-oxaspiro{4.5}decan-8-ones [ppm from $(CH_3)_4Si$]

Compd	C(2)	C(3)	C(4)	C(5)	C(6)	C(8)	C(9)	C(9')	C(10)	Other
4a	64.20	46.85	85.90	46.85	64.20	170.45	135.18	121.80	35.79	CH_3, 10.51; Ar, 142.89, 128.22, 127.83, 127.49
4b	71.73	46.85	85.90	46.85	64.20	170.41	135.10	121.98	35.65	C-$\underline{C}H_3$, 11.56; N-CH_3,42.09; Ar, 143.41, 127.14,
4c	64.13	45.48	83.91	48.02	57.03	169.97	134.96	122.09	38.40	CH_3, 10.06; Ar, 143.83, 142.82, 128.34, 128.25, 127.89, 127.54, 127.29, 126.54
4d	71.91	45.69	82.58	48.22	64.86	169.94	134.88	122.16	38.05	C-$\underline{C}H_3$, 11.16; N-CH_3, 41.50; Ar, 144.28, 143.07, 128.50, 127.18, 127.09
4e	60.64	53.18	85.74	49.23	56.85	169.70	134.98	122.16	38.96	-CH($\underline{C}H_3$), 18.51, 24.51; -$\underline{C}H(CH_3)_2$, 26.05; Ar, 143.68, 143.24, 128.95, 128.33, 128.00, 127.58, 127.27, 126.50
4f	67.88	53.50	84.40	49.69	64.27	169.70	134.92	122.23	38.66	-CH ($\underline{C}H_3)_2$, 18.58, 23.57; -$\underline{C}H(CH_3)_2$, 26.54; N-CH_3, 41.02; Ar, 144.42, 143.39, 129.51, 128.49, 127.97, 127.32, 127.05
6	81.87	46.27	84.66	46.27	81.87	170.16	134.83	122.24	35.41	CH_3, 9.80; Ar, 140.54, 128.31, 127.97, 127.34

Substituted 2,6-Diphenylpiperidin-4-ones.-The required ketones were obtained via literature procedures. Their properties corresponded to those reported.[13,14]

General Procedure for the Synthesis of the 2,6-Diphenyl-9-methylene-1-aza-7-oxaspiro[4.5]-decan-8-ones.-In a three-neck, 40 mL, round-bottomed flask, equipped with a magnetic stirrer, condenser, a pressure-equalizing addition funnel, thermometer, and a N_2 inlet, were placed activated Zn[6] (320 mesh, 0.72 g, 0.01 mol), the appropriate piperidin-4-one (0.01 mol) and dry (AR grade, kept in contact with freshly pressed sodium wire for 2 days) THF (15 mL). A solution of freshly distilled ethyl α-(bromomethyl)acrylate[7] (2.1 g, 0.01 mol) in dry THF (25 mL) was added dropwise over a period of 30 minutes while maintaining the temperature of the reaction mixture at 40-45°. The reaction mixture turned black and a slightly exothermic reaction ensued. After stirring at 45-50° for an additional 3 hours, the mixture was cooled and poured into 200 mL of ice-cold, 5% sulfuric acid. Extraction with ether (3 x 50 mL) and drying (Na_2SO_4) of the combined extracts gave a solution which was evaporated to an oil. Overnight refrigeration produced a crystalline product. Analytical samples were obtained after recrystallization (Table 1). The elemental analyses are shown below.

TABLE 5. Elemental Analyses for Compounds 4; Calcd. (Found).

Compd	Molecular Formula	C	H	N
4a	$C_{23}H_{25}NO_2$	79.50 (79.42)	7.25 (7.33)	4.03 (4.09)
4b	$C_{24}H_{27}NO_2$	79.74 (79.81)	7.53 (7.45)	3.88 (3.81)
4c	$C_{22}H_{27}NO_2$	79.25 (79.32)	6.95 (6.90)	4.20 (4.26)
4d	$C_{23}H_{25}NO_2$	79.50 (79.45)	7.25 (7.18)	4.03 (4.08)
4e	$C_{24}H_{27}NO_2$	79.74 (79.78)	7.43 (7.48)	3.88 (3.95)
4f	$C_{25}H_{29}NO_2$	79.98 (79.88)	7.79 (7.84)	3.73 (3.68)

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REFERENCES

1. H. M. Hoffmann and J. Rabe, *Angew. Chem. Intern. Ed. Engl.* **24**, 94 (1985).
2. S. M. Kupchan, R. W. Britto, M. P. Zeigler, C. J. Gilmore, R. G. Reslivo, and R.

F. Bryan, *J. Am. Chem. Soc.*, **95**, 1335 (1973); E. Rodriguez, G. H. N. Tower and J. C. Mitchell, *Phytochemistry*, **15**, 1573 (1976); L. A. Mischer, *Recent Advances in Phytochemistry*, Plenum Press: New York, Vol. 9, pp. 243-283, 1975; P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, N. N. Zawa, A. Rosowsky, S. Oppenheim, and H. Lazarus, *J. Med. Chem.*, **20**, 71 (1977); G. Schlewer, J. L. Stampf, and C. J. Benezra, *J. Med. Chem.*, **23**, 841 (1975); I. H. Hall, C. O. Starnes, Jr., K. H. Lee, and T. G. Waddell, *J. Pharm. Sci.*, **69**, 537 (1980).

3. P. A. Grieco, *Synthesis*, 67 (1975); S. S. Newaz, *Aldrichimica Acta*, **10**, 64 (1977); T. Shono and Y. Matsuyama, *J. Synth. Org. Chem., Japan*, **39**, 358 (1981); J. C. Sharma and R. P. Sharma, *Heterocycles*, **24**, 441 (1986).
4. K. Ramalingam and K. D. Berlin, *Org. Prep. Proc. Int.*, **9**, 15 (1977); D. J. O'Donnell, K. Ramalingam, K. D. Berlin, S. E. Ealick, and D. van der Helm, *J. Org. Chem.*, **43**, 4259 (1978).
5. N. S. Pantaleo, N. Satyamurthy, K. Ramarajan, D. J. O'Donnell, K. D. Berlin, and D. van der Helm, *J. Org. Chem.*, **45**, 4284 (1981); N. Satyamurthy, K. D. Berlin, D. R. Powell, and D. van der Helm, *Phosphorus & Sulfur*, **19**, 137 (1984).
6. M. S. Newman and F. J. Evans, *J. Am. Chem. Soc.*, **77**, 946 (1955).
7. K. Ramarajan, K. Ramalingam, D. J. O'Donnell, and K. D. Berlin, *Org. Synth.*, **61**, 56 (1981).
8. L. M. Jackman and S. Sternhell, *Applications of NMR Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; Chapters 1,2.
9. S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).
10. C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).
11. S. V. Venkatapathy, M. Phil. Dissertation, Bharathiar University (India), 1987.
12. K. Ramalingam, K. D. Berlin, N. Satyamurthy, and R. Sivakumar, *J. Org. Chem.*, **44**, 471 (1979).
13. M. Balasubramaniam and N. Padwa, *Tetrahedron*, **19**, 2135 (1963).
14. C. R. Noller and V. Baliah, *J. Am. Chem Soc.*, **70**, 3853 (1948).

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