UNEXPECTED ENOLIZATION OF 2-PHENYL-3-PIPERIDONE DERIVATIVES

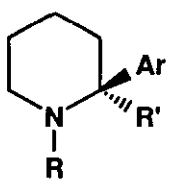
Valérie Daley,[a] Christian Cavé,*[a,b] and Jean d'Angelo*[a]

a: Unité de Chimie Organique Associé au CNRS, Centre d'Études Pharmaceutiques, Université Paris-Sud, 5 rue J.-B. Clément, 92296 Châtenay-Malabry, France

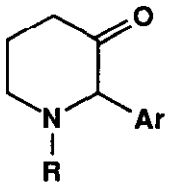
b: Laboratoire de Chimie Organique et de Chimie Thérapeutique, Faculté de Pharmacie, 7 Bld Jeanne d'Arc, 21000 Dijon, France

Abstract - Alkylation of 2-phenyl-3-piperidone (**17**) with methyl iodide or methyl acrylate furnished the 4,4-dialkylated derivatives (**18**) or (**19**), respectively. This unexpected enolization towards *the less* substituted form can be interpreted considering the appreciable steric strain which would exist in *the more* substituted enolate (**21**).

In connection with synthetic purposes in the alkaloid field,[1,2] we recently sought a direct route for the elaboration of piperidines (**1**), *gem*-disubstituted at the 2-position by an aromatic nucleus and an alkyl appendage, as found in the alkaloids karachine[3] and lycodine.[4] In our view, one particularly attractive entry to compound (**1**) might involve the alkylation, at *the more* substituted α-side of the keto group, of 2-aryl-3-piperidone derivatives (**2**) [**2** → **3**].



1

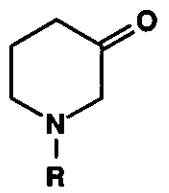


2

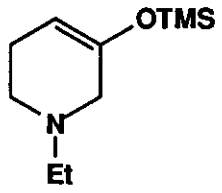
3

Since piperidones (**2**) contain a nitrogen atom at the β-position to the keto group, the effect of such a heteroatom on enolate formation should be first examined. As a matter of fact, the regioselectivity of enolization of 3-piperidones (**4**) strongly depends on the nature of the R group at the nitrogen center.[5] Thus, when R is an electron-donating group (Et), *under either kinetic or thermodynamic control conditions*, the formation of the "*distal*" enolate[5] predominates (characterized as the corresponding silyl enol ether derivative (**5**)). In sharp contrast, when R is an electron-withdrawing group (COOEt), the "*proximal* "

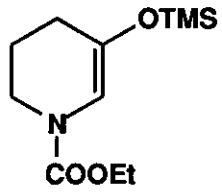
enolate[5] always predominates (characterized as **6**), regardless of the conditions of deprotonation (kinetic or thermodynamic).



4

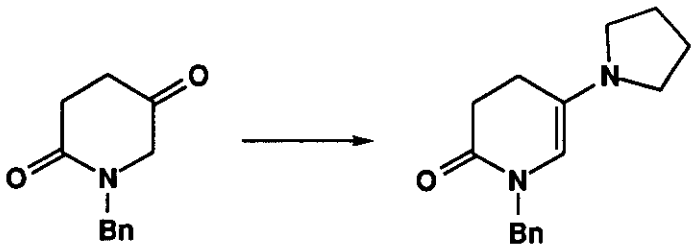


5



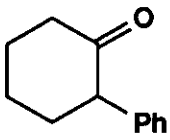
6

The exclusive formation of the *proximal* enamine (**8**) in the condensation between keto lactam (**7**) and pyrrolidine corroborates the critical effect of an electron-withdrawing group at the α-position to the nitrogen atom on the regioselectivity of enolization of 3-piperidone derivatives.[6]

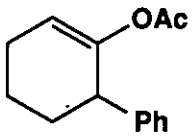


7 **8**

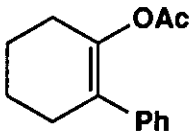
Since piperidone derivatives (**2**) bear an additional aromatic nucleus at the α-position to the keto group, the effect of such a substituent on the enolization should be also considered. Deprotonation, under *kinetic* control conditions of 2-phenylcyclohexanone (**9**), followed by enolate trapping with acetic anhydride, gave exclusively *the less* substituted enol acetate (**10**), while under *thermodynamic* conditions, *the more* substituted regioisomer (**11**) largely predominates.[7]



9



10

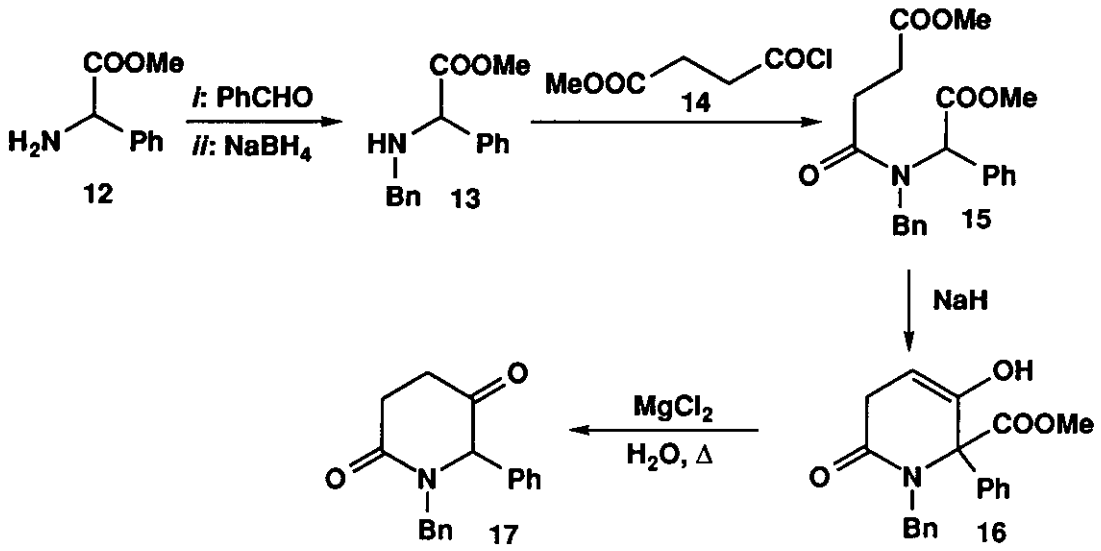


11

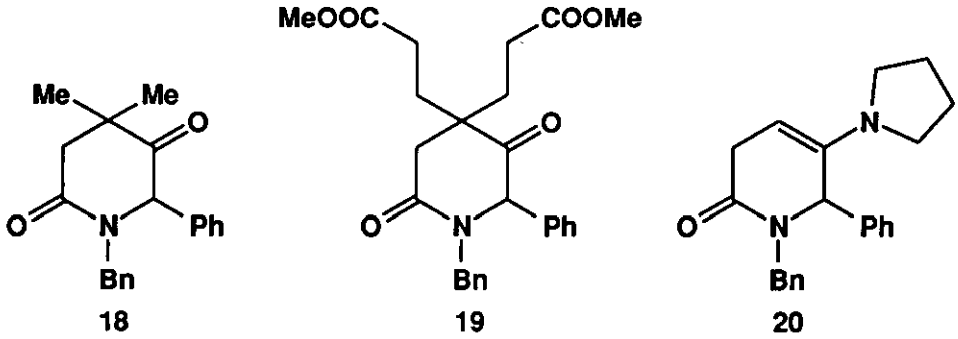
In light of the above variety of studies, we reasoned that, in keto lactam (**17**) the simultaneous presence of an electron-withdrawing group at the α-position to the nitrogen atom, and of a phenyl substituent at the 2-position, would direct enolization towards the thermodynamically-favored *more* substituted form, regiochemistry required for the conversion [**2** → **3**].

Approach to key compound (**17**) involved the following synthetic scheme, in analogy with the methodologies reported by Yamada in the indole series[8] and by Kametani in the pentazocine series.[9] First, the amino ester (**12**) was converted into benzyl derivative (**13**), which was then condensed with acid

chloride (**14**) to afford amide (**15**). NaH-induced cyclization of **15** led to lactam (**16**), *characterized as its enol form*,[10] which upon decarbomethoxylation[11] gave the desired keto lactam (**17**).

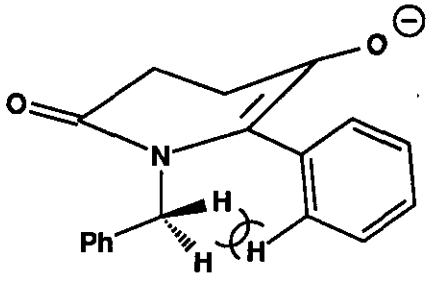


Alkylation reactions of compound (**17**), under various conditions, were next examined. Methylation of **17**, by using KH as base at 20 °C and an excess of MeI gave *gem*-dimethylated derivative (**18**) in a 70 % yield. Quite surprisingly, when 1 eq. of KH and 1 eq. of MeI were used, dimethylated derivative (**18**) was again obtained, along with recovered starting material (**17**). When LDA was used as base at - 78 °C, followed by addition of an excess of MeI, no definite compounds were isolated. Sequential treatment of **17** by Triton B in MeOH at 20 °C, and an excess of methyl acrylate afforded the *gem*-dialkylated compound (**19**) in 84 % yield. Again, when 1 eq. of methyl acrylate was used, a mixture of dialkylated derivative (**19**) and starting material (**17**) was characterized. In light of these experiments, it is clear that enolization of keto lactam (**17**) took place exclusively at *the less* substituted α-side of the keto group. A similar regiocontrol was observed by subjecting keto lactam (**17**) to pyrrolidine : *the less* substituted enamine (**20**) was exclusively formed.



The unexpected enolization of keto lactam (**17**) towards *the less* substituted form can be interpreted, considering the appreciable steric strain which would exist in the regioisomeric *more* substituted enolate

(**21**). Indeed, in order to ensure a good overlap interaction between the two moieties, the preferred conformation for the phenyl group should be coplanar to the enolate. In this conformation, there would be significant repulsions between one of the *ortho*-hydrogens of the phenyl and the benzylic hydrogens at the *N*-appendage. Thus, this steric effect may be more than large enough to overshadow the various stabilizing electronic effects at the transition state.



21

EXPERIMENTAL SECTION

General Methods. Melting points were recorded on a capillary tube melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained as neat films between NaCl plates or KBr pellets. The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise stated. Recognition of methyl, methylene, methine and quaternary carbon nuclei in ^{13}C NMR spectra rests on the *J*-modulated spin-echo sequence. Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates (0.25 mm layer). All liquid chromatography separations were performed using Merck silica gel 60 (230-400 mesh ASTM). Ether and tetrahydrofuran (THF) were distilled from Na-benzophenone ketyl. Methanol was dried over magnesium and distilled. Benzene and CH_2Cl_2 were distilled from calcium hydride. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which was flame-dried under a positive pressure of nitrogen. Organic layers were dried over anhydrous $MgSO_4$. Chemicals obtained from commercial suppliers were used without further purification. Elemental analyses were obtained from the Service de microanalyse, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France.

***N*-Benzyl-*N*-methoxypropionylsuccinic acid methyl monoester monoamide (15).** 3-Carbomethoxypropionyl chloride (4.52 g, 6.6 mmol) and Et_3N (0.76 mL, 5.5 mmol) were simultaneously added at -40 °C under nitrogen and vigourous stirring, to a solution of secondary amine (**13**) (1.42 g, 5.5 mmol) in anhydrous ether (22 mL). The resulting mixture was kept for 1 h at 0 °C, extracted with ether (3 x 25 mL), and the combined organic layers were washed with 10 % NaOH, dried and concentrated in vacuum. The residue was chromatographed over silica gel (hexane: ethyl acetate 70:30), giving **15** as a colorless solid (1.79 g, 88 %); mp: 72-74 °C (Et_2O); IR: 1744, 1657, 1607 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.3-7.0 (m, 10 H), 5.97 (s, 1H), 4.69 (d, J = 17.6 Hz, 1H), 4.44 (d, J = 17.6 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 2.8-2.5 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.1 (2C), 170.8 (C), 136.9 (C), 133.6 (C), 129.6 (2CH), 128.4 (3CH), 128.3 (2CH), 126.9 (CH), 125.9 (2CH), 62.2 (CH), 52.2

(CH_3), 51.6 (CH_3), 49.1 (CH_2), 28.9 (CH_2), 28.7 (CH_2); Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.27; H,6.27; N, 3.79. Found: C, 68.08; H, 6.39; N, 3.77.

1-Benzyl-6-methoxycarbonyl-6-phenylpiperidine-2,5-dione (16). To a suspension of 50 % NaH in oil (1.4 g, 0.029 mol) in dry dioxane (10 mL) was added lactam (**15**) (8.22 g, 0.022 mol). The resulting mixture was kept in refluxing dioxane for 7 h. After cooling, the mixture was concentrated and water was then added. The resulting mixture was thoroughly extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and concentrated under reduced pressure to give an oil which was chromatographed over silica gel (ethyl acetate: hexane 1:4) to give **16** as a colorless solid (4.41 g, 60 %); mp: 91-94 °C (AcOEt:hexane 1:4); IR: 3350-3250, 1680, 1657 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 11.70 (s, 1H), 7.4-7.15 (m, 10 H), 5.59 (d, J = 14.9 Hz, 1H), 4.08 (d, J = 14.9 Hz, 1H), 4.08 (t, J = 2.0 Hz, 1H), 3.79 (s, 3H), 3.52 (dd, J = 2.0, 19.8 Hz, 1H), 3.42 (dd, J = 2.0, 19.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7 (C), 167.3 (C), 164.9 (C), 137.1 (C), 135.8 (C), 129.1 (2CH), 128.9 (CH), 128.7 (2CH), 128.3 (2CH), 127.5 (CH), 127.2 (2CH), 92.7 (C), 62.0 (CH), 52.0 (CH_3), 46.5 (CH_2), 29.4 (CH_2); Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.67; N, 4.15. Found: C, 71.27; H, 5.73; N, 3.99.

1-Benzyl-6-phenylpiperidine-2,5-dione (17). A mixture of monoester (**16**) (1.22 g, 3.62 mmol), magnesium chloride (390 mg, 4.1 mmol) and water (0.4 mL) in dimethyl sulfoxide (4 mL) was stirred for 7.5 h at 130 °C. After cooling, the resulting mixture was poured into water, extracted with dichloromethane (3 x 25 mL), and the combined organic layers were washed with water, dried and concentrated in vacuum. The residue was chromatographed over silica gel (hexane: ethyl acetate 7:3), giving **17** as a colorless solid (0.610 g, 61 %); mp: 124-126 °C (Et_2O); IR: 1729, 1651 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.5-7.15 (m, 10 H), 5.63 (d, J = 14.7 Hz, 1H), 4.78 (s, 1H), 3.55 (d, J = 14.7 Hz, 1H), 2.9-2.7 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.4 (C), 169.7 (C), 135.7 (C), 133.9 (C), 129.1 (2CH), 128.6 (2CH), 128.4 (CH), 128.1 (2CH), 127.7 (CH), 126.3 (2CH), 68.4 (CH), 47.5 (CH_2), 34.7 (CH_2), 28.9 (CH_2); Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13; N, 5.01 Found: C, 77.19; H, 6.16; N, 5.00.

1-Benzyl-4,4-dimethyl-6-phenylpiperidine-2,5-dione (18). To a suspension of KH (40 mg, 1 mmol) in anhydrous THF (0.5 mL) under nitrogen, was added dropwise keto lactam (**17**) (92 mg, 0.33 mmol) in anhydrous THF (1 mL), and the resulting mixture was stirred for 0.5 h at 20 °C. Methyl iodide (0.22 mL, 3.5 mmol) was added and the resulting mixture was stirred for 2.5 h. 1 *N* HCl was then added and the mixture was concentrated in vacuum. Water was added and the solution was extracted with dichloromethane (3 x 25 mL), and the combined organic layers were washed with brine, dried and concentrated in vacuum. The residue was chromatographed over silica gel (hexane: ethyl acetate 3:2) to afford **18** as a colorless solid (0.07 g, 70 %); mp: 94-97 °C (Et_2O); IR: 1727, 1667, 1605 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.4-7.2 (m, 10 H), 5.70 (d, J = 14.3 Hz, 1H), 4.80 (s, 1H), 3.47 (d, J = 14.3 Hz, 1H), 2.74 (d, J = 13.4 Hz, 1H), 2.57 (d, J = 13.4 Hz, 1H), 1.18 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (50 MHz. $CDCl_3$) δ 207.2 (C), 169.2 (C), 135.9 (C), 134.1 (C), 129.2 (3CH), 128.8 (3CH), 128.6 (CH),

128.4 (CH),126.6 (2CH), 67.0 (CH), 47.5 (CH_2), 42.9 (C), 42.8 (CH_2), 24.8 (CH_3), 24.5 (CH_3); Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.88; N, 4.55 Found: C, 77.95; H, 6.94; N, 4.50.

Dimethyl 1-benzyl-2,5-dioxo-6-phenyl-4,4-piperidine dipropionate (19). To a solution of keto lactam (**17**) (0.11 g, 0.394 mmol) in anhydrous THF (2 mL) was added at 20 °C a solution of Triton B (20 mL, 40 % in MeOH, 0.045 mmol) and methyl acrylate (0.1 mL, 1.1 mmol). The resulting mixture was stirred during 24 h at 20 °C. 1 *N* HCl was then added and the mixture was concentrated in vacuum. Water was added and the solution was extracted with ether (3 x 25 mL), and the combined organic layers were washed with brine, dried and concentrated in vacuum. The residue was chromatographed over silica gel (hexane: ethyl acetate 3:2) to afford **19** as an oil (0.149 g, 84 %); IR: 1740, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45-7.2 (m, 10 H), 5.61 (d, J = 14.4 Hz, 1H), 4.79 (s, 1H), 3.63 (s, 3H), 3.56 (d, J = 14.4 Hz, 1H), 3.55 (s, 3H), 2.75 (d, J = 16.2 Hz, 1H), 2.54 (d, J = 16.2 Hz, 1H), 2.4-2.1 (m, 2H), 2.0-1.55 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.1 (C), 172.5 (C), 172.2 (C), 168.5 (C), 135.5 (C), 133.1 (C), 129.1 (2CH), 128.7 (3CH), 128.4 (2CH), 128.2 (CH),126.2 (2CH), 67.4 (CH), 51.5 ($2CH_3$), 48.1 (C), 47.7 (CH_2), 38.0 (CH_2), 30.9 (CH_2), 28.9 (CH_2), 28.2 (CH_2), 28.0 (CH_2).

1-Benzyl-2-oxo-5-pyrrolidinyl-6-phenyl-1,2,3,6-tetrahydropyridine (20). In a flask fitted with a Dean-Stark system, a mixture of keto lactam (**17**) (170 mg, 0.6 mmol), benzene (5 mL), pyrrolidine (50 mL, 0.6 mmol) and a catalytic amount of *p*-TsOH was refluxed for 24 h. The resulting mixture was concentrated under reduced pressure (10^{-1} Torr) to give the crude enamine (**20**) as an oil; IR: 1656 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.3-6.9 (m, 10 H), 5.82 (d, J = 14.8 Hz, 1H), 4.77 (s, 1H), 4.15 (t, J = 3.7 Hz, 1H), 3.43 (d, J = 14.8 Hz, 1H), 3.35-3.3 (m, 2H), 2.6-2.3 (m, 4H), 1.2-1.0 (m, 4H); ^{13}C NMR (50 MHz, C_6D_6) δ 168.6 (C), 142.8 (C), 140.8 (C), 138.0 (C), 129.3-126.9 (10CH), 89.2 (CH), 61.7 (CH), 47.9 ($2CH_2$), 46.4 (CH_2) 32.6 (CH_2), 24.6 ($2CH_2$).

REFERENCES

1. D. Desmaële and J. d'Angelo, *J. Org. Chem.*, 1994, **59**, 2292.
2. D. Desmaële, K. Mekouar, and J. d'Angelo, *J. Org. Chem.*, 1997, **62**, 3890.
3. R. V. Stevens and J. R. Pruitt, *J. Chem. Soc., Chem. Commun.*, 1983, **23**, 1423.
4 E. Kleinman and C. H. Heathcock, *Tetrahedron Lett.*, 1979, 4125.
5. V. A. Martin, D. H. Murray, N. E. Pratt, Y. Zhao, and K. F. Albizati, *J. Am. Chem. Soc.*, 1990, **112**, 6965.
6. J. Bonjoch, J. Quirante, I. Serret, and J. Bosch, *Tetrahedron Lett.*, 1989, **30**, 1861.
7. B. Miller and H-S. Wong, *Tetrahedron*, 1972, **28**, 2369.
8. T. Shioiri and S. Yamada, *Tetrahedron*, 1968, **24**, 4159.
9. T. Kametani, S.-P. Huang, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, 1975, **23**, 2010.
10. For a related unusal tautomerization, see: L. Ambroise, C. Chassagnard, G. Revial, and J. d'Angelo, *Tetrahedron: Asymmetry*, 1991, **2**, 407.
11. T. Kametani, N. Kanaya, and M. Ihara, *J. Chem. Soc., Perkin Trans I*, 1981, 959.

Received, 29th June, 1998