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THE FISCHER INDOLIZATION OF 4-ACETONYL-2,6-PIPERIDINEDIONES

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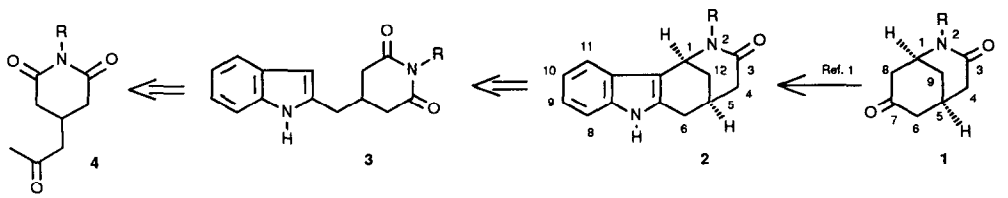
Abstract. The PPA induced Fischer indolization of 4-acetonyl-2,6-piperidinediones **4** takes place both at the methylene and the methyl carbons, although the latter regioisomer (**3**) undergoes a further cyclization of the imide moiety upon the indole 3-position followed by ring-opening of the resulting intermediate **9** to give tetrahydrocarbazolone **8**. Fragmentation of the two possible regioisomers **3** and **7** to 2-methylindole occurs at higher temperatures. This process is more pronounced when using 4-acetonyl-3,4-dihydro-2(1*H*)-pyridone **13** as the substrate for the indolization. The use of *N*-acetylphenylhydrazone derivatives leads to similar results as a consequence of the deacylation of the initially formed indole derivatives. In this case, an additional *C*-acylation of the indole ring also occurs.

In a previous paper[1] we have reported that the Fischer indolization of azabicyclodiones **1** (R=CH_3, CH_2CH_2OAc) affords mixtures of the two possible regioisomers in which the desired tetracyclic lactam **2**, possessing four of the five rings of pentacyclic *Strychnos* indole alkaloids,[2] was the minor compound. Our interest in lactam **2** (R=CH_2CH_2OAc) lies in the fact that it can allow the evaluation of the effect of the endocyclic amide carbonyl group on the cyclization upon the indole 3-position, which would afford a pentacyclic *Strychnos* type system.[3] 4-(2-Indolylmethyl)-2,6-piperidinediones of type **3** were envisaged as alternative potential precursors of **2**. For this reason we decided to investigate the Fischer indolization of 4-acetonyl-2,6-piperidinediones **4**.[4] We present here the results of this study.



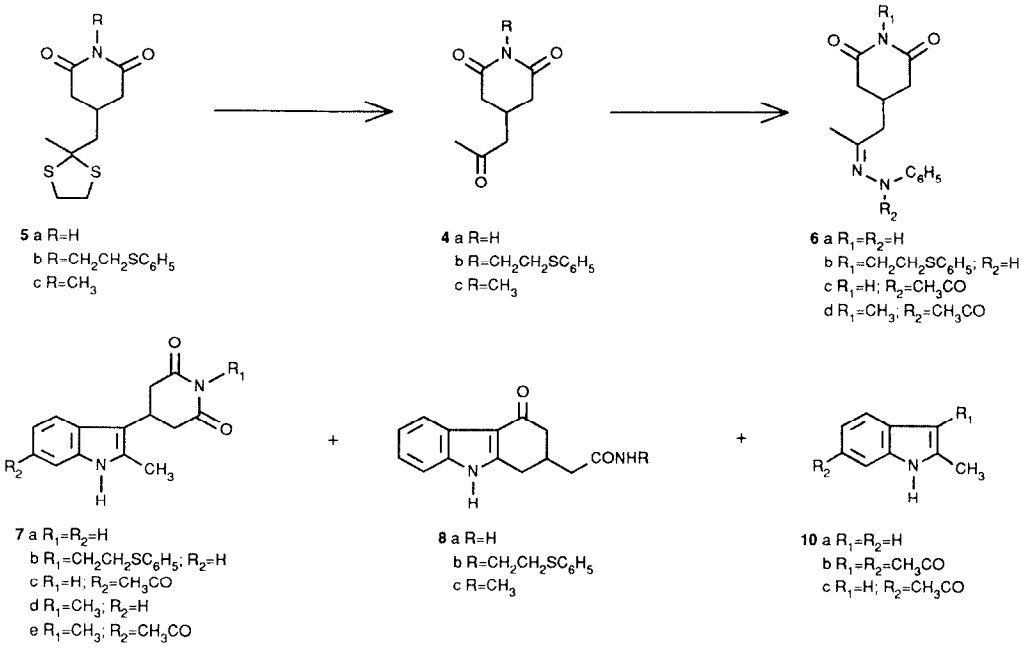
SCHEME 1

RESULTS

The required ketones **4a-c** (Scheme 2) were obtained in high yields from the corresponding dithioacetals **5a-c**[1] by treatment with $HgCl_2$/HgO in aqueous methanolic solution. It is well known[5] that PPA is the catalyst

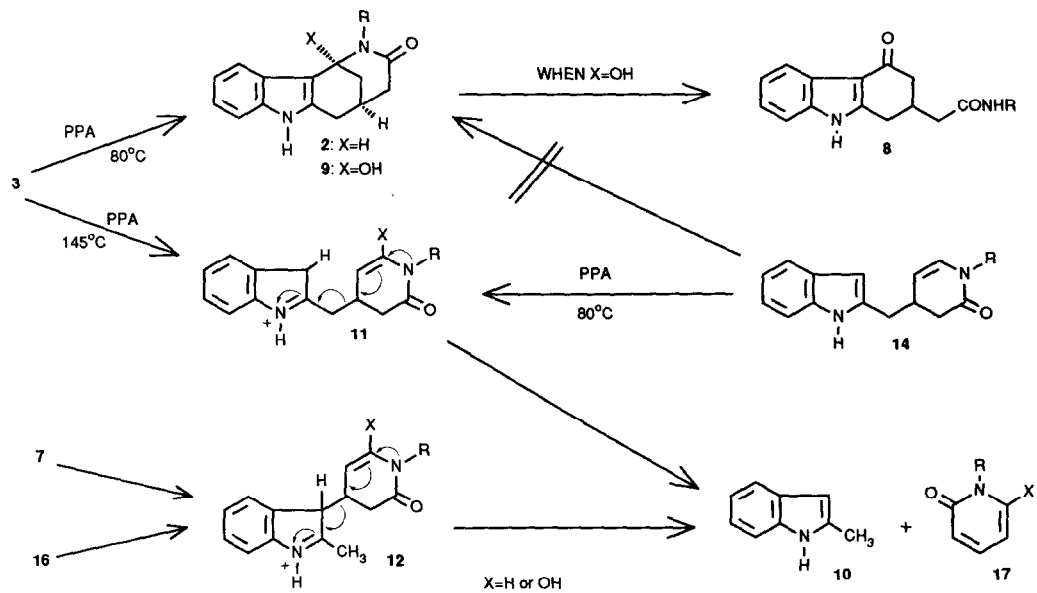
of choice when the Fischer indolization of an unsymmetrically substituted ketone involving a methyl group is required. However, treatment of phenylhydrazone **6a**, derived from **4a**, with an excess of PPA at 80°C for 1 h afforded a mixture of 4-(3-indolyl)piperidinedione **7a** (28% yield), in which the indolization had occurred upon the methylene carbon, and carbazolone **8a** (64% yield).[6] Similarly, when phenylhydrazone **6b** was used as the substrate for the Fischer indolization, a mixture of **7b** and **8b** was obtained. Formation of the unexpected compounds **8a** and **8b** can be accounted for by considering that the Fischer indolization has taken place, in part, with the expected regioselectivity but that, under the acidic reaction conditions, the desired major isomers **3** undergo cyclization, via an acyliminium cation, to tetracyclic hydroxylactams **9** and further irreversible ring-opening as depicted in Scheme 3. Although formation of carbazolones **8** by direct cyclization upon the indole 3-position of an acylium cation generated from the imide moiety can not be excluded, the presence of the unaffected glutarimide unit in compounds **7a** and **7b** supports the mechanism above proposed.

On the other hand, when the indolization of **6a** was effected with PPA at a higher temperature (145°C for 45 min), 2-methylindole (**10a**) was obtained as the only identifiable product. This result made evident that, under these more drastic reaction conditions, the two possible regioisomeric indole derivatives **3** (R=H) and **7a**, initially formed after the Fischer indolization, undergo fragmentation of the carbon-carbon bond exocyclic to the glutarimide ring, probably through the enol form of one imide carbonyl group in intermediates [**11** (X=OH) and **12** (X=OH), respectively] in which the indole ring is protonated (see Scheme 3). In fact, in a separate experiment, **7a** was fully converted into 2-methylindole (**10a**) by treatment with PPA at 145°C.



SCHEME 2

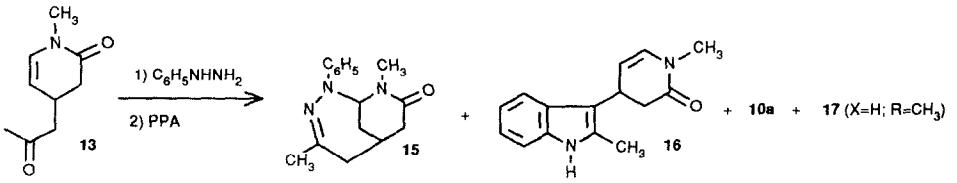
The deactivation of the indole nucleus as 1-acetyl derivative was envisaged as a possible way of retarding or inhibiting both the acid-catalyzed cyclization of the imide moiety and the protonation of the indole ring in the hypothetical intermediate **3**. Since there are some precedents for the preparation of 1-acylindoles by Fischer indole synthesis from *N*-acetylphenylhydrazones,[7] we decided to study the Fischer indolization of **6c**. However, when this hydrazone was treated with PPA at 100°C for 30 min, a complex mixture was formed. After column chromatography, the following indole derivatives were isolated:[8] carbazolone **8a** (13%), 4-(3-indolyl)piperidinediones **7a** (<5%) and **7c** (10%), and 2-methylindoles **10b** (28%) and **10c** (5%). No 1-acylindole derivatives were detected. This result again points out that the desired regioisomer is formed to some extent but that at 100°C both cyclization-ring opening to give a carbazolone system and fragmentation affording 2-methylindole occur, probably after deacylation of the indole nitrogen. The formation of *C*-acetylindoles **7c**, **10b**, and **10c**[9] can be accounted for by considering a transacylation from the initially formed 1-acetylindoles. Similar mixtures containing only *N*-deacetylated derivatives (carbazolone **8c** and 4-(3-indolyl)piperidinediones **7d** and **7e**) were obtained when *N*-acetylhydrazone **6d** was subjected to the Fischer indole synthesis (PPA, 100°C, 30 min).



SCHEME 3

Since *N*-acylation of phenylhydrazone did not avoid the undesired cyclization-ring opening (**3**→**9**→**8**) that precluded the isolation of the expected 4-(indolylmethyl)piperidinedione **3**, we decided to take advantage of this cyclization by using enamido ketone **13**[1] as the starting material for the Fischer indolization. We anticipated that, after indole formation, cyclization of the acyliminium ion generated by protonation of the enamide moiety of **14** (R=CH_3) would afford, in a one-pot reaction, the desired tetracyclic system **2** (Scheme

3). However, treatment of phenylhydrazone derived from ketone **13** with PPA at 80°C for 30 min again afforded a complex reaction mixture in which the expected tetracyclic compound **2** (R=CH_3) could not be detected. Careful chromatographic separation allowed the isolation, although in low yields, of triazabicyclo **15**, 2,3-disubstituted indole **16**, 2-methylindole (**10a**), and 2-pyridone **17** (R=CH_3, X=H) (Scheme 4). Formation of **15** simply implies the nucleophilic attack of one hydrazino nitrogen upon the acyliminium cation generated by protonation of the enamide function. The isolation of the fragmentation products **10a** and **17** (R=CH_3, X=H) under a set of reaction conditions (PPA, 80°C, 30 min) that did not promote fragmentation in the above glutarimide series reflects the greater tendency of the hypothetical intermediate **11** to undergo fragmentation when X=H than when X=OH, probably due to the presence of the enamide carbon-carbon double bond.



SCHEME 4

Although not encouraging from a synthetic standpoint, the results here reported offer some unprecedented reactions of 2,6-piperidinediones and dihydro-2-pyridones having 2-indolylmethyl or 3-indolyl substituents at the 4-position.

EXPERIMENTAL PART

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Varian XL-200 (200 MHz) or with a Perkin-Elmer R-24 (60 MHz) spectrometer. ^{13}C-NMR spectra were recorded on a Varian XL-200 (50.3 MHz) spectrometer. Unless otherwise indicated, NMR spectra were measured in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) downfield from TMS as internal standard. IR spectra were taken with a Perkin-Elmer 1430 spectrophotometer, and only noteworthy absorptions (cm^{-1}) are listed. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60, 0.063-0.200 mm or 0.040-0.063 mm). Thin layer chromatography was done on Merck silica gel 60 F_{254} aluminum precoated sheets, and the spots were located with UV light or iodoplatinate reagent. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate. Microanalyses were performed by Instituto de Química Bio-Orgánica, Barcelona.

4-Acetonyl-1-[2-(phenylthio)ethyl]-2,6-piperidinedione Ethylenedithioacetal (5b). A sodium hydride oil dispersion (55-60%, 190 mg, 4.7 mmol) was washed under nitrogen with anhydrous hexane (3 x 5 ml) and the residue was covered with DMF (25 ml). To this suspension, a solution of imide **5a**[1] (1 g, 4.0 mmol) in

anhydrous DMF (50 ml) was added and the resulting mixture was stirred at 0^0C for 1 h. After this time, 1-bromo-2-(phenylthio)ethane (975 mg, 4.5 mmol) was slowly added and stirring was continued for 3 h at room temperature. The reaction mixture was poured into cold water and concentrated under vacuum affording a residue which was dissolved in $CHCl_3$. The organic layer was washed with brine, dried, and evaporated to give an oil which was purified by flash chromatography. Elution with 1:1 $CHCl_3$:C_6H_6 gave **5b** (1.5 g, 96%) as a white solid: ^{1}H-NMR (60 MHz) 1.7 (s, 3H, CH_3), 2.9 (m, 2H, $C_6H_5SCH_2$),3.2 (s, 4H, $S(CH_2)_2S$), 3.8 (m, 2H, N-CH_2), 6.9-7.3 (m, 5H, C_6H_5); ^{13}C-NMR 27.8 (C-4), 30.4 (ArSCH_2), 33.9 (CH_3), 39.1 (NCH_2), 40.1 (SCH_2), 40.2 (C-3), 48.9 (CH_2), 65.5 (SCS), 126.0 (*p*-Ar), 128.7 (*o*-Ar), 129.0 (*m*-Ar), 135.7 (*i*-Ar), 171.7 (C=O); mp 70-71°C (ethanol); (Found: C, 56.59; H, 6.17; N, 3.54; S, 25.00. Calcd. for $C_{18}H_{23}NO_2S_3$: C, 56.66; H 6.07; N, 3.67; S, 25.20).

4-Acetonyl-2,6-piperidinediones 4. General Procedure for the Cleavage of Dithioacetals 5. To a solution of dithioacetals **5**[1] (20 mmol) in 4:1 methanol-water (250 ml) were added mercuric chloride (44 mmol) and mercuric oxide (22 mmol). The resulting mixture was refluxed for 3 h with rapid stirring under nitrogen atmosphere. The cold mixture was filtered and the solid residue was washed with 4:1 methanol-water. Then, 20% aqueous ammonium polysulfide was slowly added to the above solution until the formation of a black precipitate was not observed. The solid was removed by filtration through a Hyflo-Super Cel pad and the filtrate was concentrated under reduced pressure. The resulting residue was digested with ethyl acetate and the solution was dried and evaporated to dryness. **4-Acetonyl-2,6-piperidinedione (4a)** (94%): ^{1}H-NMR (200 MHz) 2.17 (s, 3H, CH_3CO); 2.32 (m, 2H, H-3ax and H-5ax), 2.55 (d, *J*=6.2 Hz, 2H, CH_2CO), 2.50-2.80 (m, 1H, H-4), 2.75, (dm, *J*=17.5 Hz, 2H, H-3eq and H-5eq), 8.40 (br s, 1H, NH); ^{13}C-NMR 25.7 (C-4), 30.4 (CH_3), 37.3 (C-3), 47.4 (CH_2), 172.1 (CO imide), 205.6 (CO ketone); IR (KBr) 3180 and 3070 (NH), 1720 and 1680 (C=O); mp 144-145°C (ethanol); (Found: C, 56.76; H, 6.59; N, 8.20. Calcd. for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.28). **4-Acetonyl-1-[2-(phenylthio)ethyl]-2,6-piperidinedione (4b)** (89%): ^{1}H-NMR (200 MHz) 2.14 (s, 3H, CH_3CO), 2.25 (m, 2H, H-3ax and H-5ax), 2.2-2.6 (m, 1H, H-4), 2.50 (br s, 2H, CH_2CO), 2.75 (dm, *J*=16.8 Hz, 2H, H-3eq and H-5eq), 3.05 (t, *J*=7.0 Hz, 2H, CH_2S), 3.95 (t, *J*=7.0 Hz, 2H, CH_2N), 7.05-7.40 (m, 5H, Ar); bp 250°C (10^{-1} mm Hg); (Found: C, 62.64; H, 6.78; N, 4.60; S, 10.37. Calcd. for $C_{16}H_{19}NO_3S$: C, 62.92; H, 6.27; N, 4.58; S, 10.49). **4-Acetonyl-1-methyl-2,6-piperidinedione (4c)** (89%): ^{1}H-NMR (200 MHz) 2.17 (s, 3H, CH_3CO), 2.37 (m, 2H, H-3ax and H-5ax), 2.54 (dm, *J*=6.2 Hz, 2H, CH_2CO), 2.50-2.80 (m, 1H, H-4), 2.84 (dm, *J*=17.5 Hz, 2H, H-3eq and H-5eq), 3.13 (s, 3H, CH_3N); ^{13}C-NMR 24.5 (C-4), 26.0 (CH_3N), 30.1 (CH_3CO), 37.9 (C-3), 47.2 (CH_2CO), 171.5 (CO imide), 205.4 (CO ketone); IR ($CHCl_3$) 1720 and 1670 (C=O); bp 150°C (1 mm Hg); (Found: C, 59.25; H, 7.16; N, 7.56. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.64).

Phenylhydrazones 6a and 6b. To a solution of ketones **4a** or **4b** (5.5 mmol) in absolute ethanol (30 ml) was added phenylhydrazine (5.5 mmol) and the mixture was refluxed for 3 h. The solvent was evaporated under vacuum and the resulting solid was crystallized from ethanol. **6a**:^{1}H-NMR (CD_3OD-$CDCl_3$, 60 MHz) 1.8 (s, 3H, CH_3), 6.5-7.3 (m, 5H, C_6H_5); IR ($CHCl_3$) 3320 (NH hydrazone), 3180 and 3060 (NH imide), 1710 and 1680 (C=O), 1590 (C=N); mp 149-151°C (ethanol); (Found: C, 64.72; H, 6.61; N, 16.29. Calcd. for $C_{14}H_{17}N_3O_2$: C, 64.84; H, 6.60; N, 16.20). **6b**: ^{1}H-NMR (60 MHz) 1.7 (s, 3H, CH_3), 2.9 (m, 2H, SCH_2), 3.8

(m, 2H, NCH_2), 6.5-7.4 (m, 10H, $2C_6H_5$); IR ($CHCl_3$) 3360 (NH), 1730 and 1680 (C=O), 1600 (C=N).

Phenylhydrazones 6c and 6d. A solution of the ketone **4a** or **4c** (12.0 mmol) and *N*-phenylacetohydrazide[7a] (12.0 mmol) in dioxane (80 ml) was refluxed for 24 h. The solvent was evaporated under vacuum and the resulting solid was used in the Fischer indolization without further purification.

Fischer Indolization of 6a. Phenylhydrazone **6a** (2 g, 7.7 mmol) was treated with an excess of PPA at 80°C with vigorous stirring for 1 h. The cooled mixture was poured into ice-water, basified with concentrated NH_4OH, and extracted with ethyl acetate. Evaporation of the extracts gave a solid which was chromatographed. Elution with 9:1 $CHCl_3$:C_6H_6 afforded 0.53 g (28%) of **4-(2-methyl-3-indolyl)-2,6-piperidinedione** (**7a**): ^{1}H-NMR (200 MHz) 2.41 (s, 3H, ArCH_3), 2.82 (dm, *J*=17.6 Hz, 2H, H-3eq and H-5eq), 3.20 (dd, *J*=17.6 and 14.0 Hz, 2H, H-3ax and H-5ax), 3.55 (m, 1H, H-4), 7.10 (m, 2H, H-5ind and H-6ind), 7.30 and 7.50 (2d, 2H, H-4ind and H-7ind), 7.90 (br s, 1H, NH imide), 8.05 (br s, 1H, NHind); IR (KBr) 3380 (NHind), 3180 and 3070 (NH imide), 1720 and 1680 (C=O); mp 238-239°C (ethanol-diethyl ether); (Found:C, 69.64; H, 5.83; N, 11.48. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.59). Elution with 9:1 $CHCl_3$:CH_3OH afforded 1.2 g (64%) of **4-oxo-1,2,3,4-tetrahydro-2-carbazoleacetamide** (**8a**): ^{1}H-NMR (DMSO-d_6, 200 MHz) 2.25 (d, *J*=6.5 Hz, 2H, CH_2CONH_2), 2.20-3.20 (m, 5H, H-1, H-2, and H-3), 6.90 (br s, 2H, $CONH_2$), 7.15, 7.40, and 7.95 (3m, 4H, Ar), 11.85 (br s, NHind); ^{13}C-NMR 28.4 (C-1), 33.2 (C-2), 40.6 (CH_2CONH_2), 43.9 (C-3), 111.5 (C-4a), 111.6 (C-8), 120.1 (C-5), 121.5 (C-6), 122.4 (C-7), 124.4 (C-4b), 136.1 (C-8a), 151.5 (C-9a), 172.8 ($CONH_2$), 192.0 (CO); IR (KBr) 3000-3300 (NH), 1620 (C=O); mp 283-284°C (methanol); (Found: C, 69.35; H, 5.75; N, 11.37. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.59).

Fischer Indolization of 6b. Operating as above, phenylhydrazone **6b** (1.5 g, 3.8 mmol) afforded a mixture of **4-(2-methyl-3-indolyl)-1-[2-(phenylthio)ethyl]-2,6-piperidinedione** (**7b**) (0.32 g, 22%): ^{1}H-NMR (60 MHz) 2.3 (s, 3H, CH_3); 2.6-3.4 (m, 6H, imide and SCH_2), 3.9 (m, 2H, NCH_2), 6.7-7.3 (m, 9H, Ar), 7.7 (br s, 1H, NHind); IR ($CHCl_3$) 3450 (NH), 1720 and 1670 (C=O) cm^{-1} and ***N*-[2-(phenylthio)ethyl]-4-oxo-1,2,3,4-tetrahydro-2-carbazoleacetamide** (**8b**) (0.94 g, 65%): ^{1}H-NMR (DMSO-d_6, 200 MHz) 2.26 (d, *J*=6.5 Hz, 2H, CH_2CONH), 2.20-3.10 (m, 5H, H-1, H-2, and H-3), 3.00 (t, *J*=7.0 Hz, 2H, CH_2S), 3.25 (t, *J*=7.0 Hz, 2H, CH_2N), 6.80-7.20 (m, 8H, Ar), 7.62 (m, 1H, Ar), 7.86 (br s, 1H, CONH), 11.30 (br s, 1H, NHind); ^{13}C-NMR (DMSO-d_6) 28.5 (C-1), 31.8 (CH_2S), 33.4 (C-2), 38.3 (CH_2N), 40.9 (CH_2CONH), 43.9 (C-3), 111.5 (C-4a), 111.7 (C-8), 120.2 (C-5), 121.7 (C-6), 122.6 (C-7), 124.4 (C-4b), 125.8 (*p*-Ar), 128.3 (*o*-Ar), 129.2 (*m*-Ar), 135.7 (*i*-Ar), 136.2 (C-8a), 151.6 (C-9a), 170.9 (CON), 192.1 (CO); IR (KBr) 3000-3300 (NH), 1620 (C=O); mp 236-238°C (ethanol); (Found:C, 69.65; H, 5.88; N, 7.40. Calcd. for $C_{22}H_{22}N_2O_2S$:C, 69.81; H, 5.85; N, 7.40).

Fischer Indolization of 6c. Operating as above, from phenylhydrazone **6c** (1 g, 3.3 mmol) and PPA for 30 min at 100°C, the following compounds were isolated after flash chromatography (96:4 AcOEt-EtOH): **7a** (22 mg, *ca.* 5%); **8a** (100 mg, 13%); **4-(6-acetyl-2-methyl-3-indolyl)-2,6-piperidinedione** (**7c**) (90 mg, 10%): ^{1}H-NMR (200 MHz) 2.40 (s, 3H, $ArCH_3$), 2.66 (s, 3H, CH_3CO), 2.80 (dm, *J*=17.0 Hz, 2H, H-3eq and H-5eq), 3.15 (dd, *J*=17.0 and 14.0 Hz, 2H, H-3ax and H-5ax), 3.60 (m, 1H, H-4), 7.32 (d, *J*=8.5 Hz, 1H,

H-4ind), 7.78 (dd, *J*=8.5 and 1.5 Hz, 1H, H-5ind), 8.20 (d, *J*=1.5 Hz, 1H, H-7ind); MS, *m/e* (relative intensity) 284 (M^+, 32), 269 (24), 242 (26), 215 (17), 200 (25), 199 (27), 184 (54), 93 (100); **3,6-diacetyl-2-methylindole (10b)** (200 mg, 28%): ^{1}H-NMR (DMSO-d_6, 200 MHz) 2.53, 2.58, and 2.69 (3s, 9H, $3CH_3$), 7.42 (dd, *J*=8.5 and 0.6 Hz, 1H, H-4), 7.77 (dd, *J*=8.5 and 1.6 Hz, 1H, H-5), 8.68 (dd, *J*=1.6 and 0.6 Hz, 1H, H-7), 12.1 (br s, 1H, NH), IR (KBr) 3350-3000 (N-H), 1680 (C=O), 1620 (C=O); **6-acetyl-2-methylindole (10c)** (30 mg, *ca.* 5%): ^{1}H-NMR (200 MHz) 2.46 (d, *J*=1.0 Hz, 3H, $ArCH_3$), 2.65 (s, 3H, CH_3CO), 6.32 (m, 1H, H-3), 7.29 (dm, *J*=8.5 Hz, 1H, H-4), 7.80 (dd, *J*=8.5 and 1.7 Hz, 1H, H-5), 8.18 (d, *J*=1.7 Hz, 1H, H-7), 8.25 (br s, 1H, NH); IR (KBr) 3100-3500 (NH), 1670 (C=O).

Fischer Indolization of 6d. Operating as above, phenylhydrazone **6d** (860 mg, 2.7 mmol) afforded a mixture of the following compounds: **1-methyl-4-(2-methyl-3-indolyl)-2,6-piperidinedione (7d)** (20 mg, 3%): ^{1}H-NMR (200 MHz) 2.60 (s, 3H, $ArCH_3$), 3.12 (dm, *J*=17.6 Hz, 2H, H-3eq and H-5eq), 3.45 (dd, *J*=17.6 and 14.0 Hz, 2H, H-3ax and H-5ax), 3.44 (s, 3H, N-CH_3), 3.75 (m, 1H, H-4), 7.30 (m, 2H, H-5ind and H-6ind), 7.50 (m, 1H, H-7ind), 7.70 (m, 1H, H-4ind), 8.15 (br s, 1H, NH); IR (KBr) 3380 (NH), 1710 and 1680 (C=O); **4-(6-acetyl-2-methyl-3-indolyl)-1-methyl-2,6-piperidinedione (7e)** (240 mg, 34%): ^{1}H-NMR (CD_3OD, 200 MHz) 2.42 (s, 3H, $ArCH_3$), 2.65 (s, 3H, CH_3CO), 2.84 (dd, *J*=17.0 and 4.0 Hz, 2H, H-3eq and H-5eq), 3.20 (s, 3H, NCH_3), 3.33 (tm, *J*=17.0 Hz, 2H, H-3ax and H-5ax), 3.65 (m, 1H, H-4), 7.32 (d, *J*=8.5 Hz, 1H, H-4ind), 7.74 (dd, *J*=8.5 Hz, 1H, H-5ind), 8.30 (d, *J*=1.5 Hz, 1H, H-7ind); ^{13}C-NMR 11.9 ($ArCH_3$), 26.8 (NCH_3 and CH_3CO), 27.9 (C-4), 39.3 (C-3), 111.3 (C-4ind), 120.4 (C-7ind), 122.2 (C-5ind), 174.1 (C-2), 200.6 (ArCO); IR (KBr) 3350 (NH), 1710, 1680, and 1660 (C=O); mp 218-220°C (ethanol); (Found: C, 68.33; H, 6.23; N, 9.01. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39); ***N*-methyl-4-oxo-1,2,3,4-tetrahydro-2-carbazoleacetamide (8c)** (138 mg, 20%): ^{1}H-NMR (DMSO-d_6, 200 MHz) 2.25 (d, *J*=6.5 Hz, 2H, CH_2CONH_2), 2.20-3.10 (c s, 5H, H-1, H-2, and H-3), 2.57 and 2.60 (2s, $CONHCH_3$), 7.15, 7.40, and 7.95 (3m, 4H, Ar), 7.80 (br s, 1H, CONH), 11.85 (br s, 1H, NHind); ^{13}C-NMR (DMSO-d_6) 25.4 (CH_3N), 28.4 (C-1), 33.3 (C-2), 38.3 (CH_2CO), 43.9 (C-3), 111.5 (C-4a), 111.6 (C-8), 120.1 (C-5), 121.5 (C-6), 122.4 (C-7), 124.3 (C-4b), 136.0 (C-8a), 151.5 (C-9a), 170.9 (CON), 191.9 (CO); IR (KBr) 3080-3300 (NH) and 1610-1670 (C=O); mp 273-275°C (methanol); (Found: C, 70.21; H, 6.27; N, 10.68. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.28; N, 10.93).

Fischer Indolization of 4-acetonyl-1-methyl-3,4-dihydro-2(1*H*)-pyridone (13). A solution of ketone **13**[1] (1.9 g, 11.4 mmol) and phenylhydrazine (1.23 g, 11.4 mmol) in ethanol was refluxed for 20 h. The solvent was evaporated under vacuum and the resulting solid was treated with an excess of PPA at 80°C for 30 min. After the usual work-up, the reaction mixture was chromatographed affording 2-methylindole and *N*-methyl-2-pyridone along with the following compounds: **1-Methyl-4-(2-methyl-3-indolyl)-3,4-dihydro-2(1*H*)-pyridone (16)** (135 mg, 5%): ^{1}H-NMR (200 MHz) 2.36 (s, 3H, $ArCH_3$), 2.63 (ddd, *J*=16.6, 6.6, and 1.4 Hz, 1H, H-3eq), 2.92 (dd, *J*=16.6 and 13.6 Hz, 1H, H-3ax), 3.15 (s, 3H, CH_3N), 4.10 (m, 1H, H-4), 5.32 (ddd, *J*=7.5, 2.5, and 1.4 Hz, 1H, H-5), 6.15 (dd, *J*=7.5 and 3.0 Hz, 1H, H-6), 7.0-7.6 (m, 4H, Ar), 8.05 (br s, 1H, NH); IR ($CHCl_3$) 3460 (NH) and 1650 (C=O); MS, *m/e* (relative intensity) 240 (M^+, 100), 225 (54), 211 (18), 197 (51), 184 (30), 183 (67), 182 (22), 168 (46), 167 (32), 154 (36), 147 (17), 144 (13), 143 (12), 131 (14), 130 (30), 124 (16), 110 (27); **4,9-Dimethyl-2-phenyl-2,3,9-triazabicyclo[4.3.1]dec-3-en-8-one**

(15) (440 mg, 15%): ^{1}H-NMR (200 MHz) 2.16 (s, 3H, CH_3C=), 2.05-2.50 (m, 5H, H-5, H-6, and H-10), 2.53 (s, 3H, CH_3N), 2.50-2.60 (m, 2H, C-7), 5.41 (m, 1H, H-1), 6.92 (m, 1H, *p*-Ar), 7.27 (m, 4H, *o*-Ar and *m*-Ar); ^{13}C-NMR 23.5 (C-6), 27.2 (CH_3C=), 33.5 (CH_3N), 35.7* (C-10), 36.5* (C-5), 40.4 (C-7), 72.2 (C-1), 115.1 (*o*-Ar), 120.8 (*p*-Ar), 129.0 (*m*-Ar), 152.0 (*i*-Ar), 162.0 (C=N), 169.5 (C=O); IR ($CHCl_3$) 1640 (C=O) and 1595 (C=N); MS, *m/e* (relative intensity) 257 (M^+, 10), 148 (16), 123 (19), 111 (11), 110 (100), 106 (26), 92 (11), 91 (14).

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9.The formation of **10c**, carrying an acetyl substituent at C-6 rather than at the more nucleophilic 3-position, suggests that this compound is formed by fragmentation of **7c**.