PREPARATION AND REACTIVITY OF 1-BENZYL-2,4-PIPERIDINEDIONE-3-CARBOXYLIC ACID DERIVATIVES

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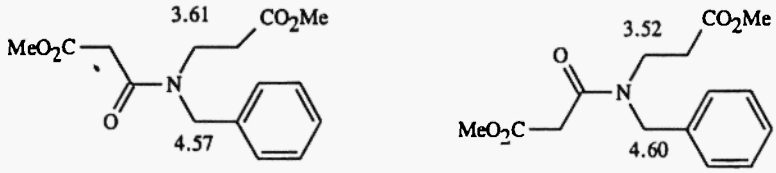
Abstract- The preparation and structural determination of 2,4-piperidinedione-3-carboxylic acid methyl ester **4** by a Dieckmann reaction was reported. Decarbomethoxylation and alkylation studies on **4** were also reported.

The 4-piperidone framework has been used as synthetic intermediates specially in the synthesis of natural products and compounds with pharmacological interest (1), while synthetic applications of 2,4-piperidinedione derivatives have been reported in the preparation of emetine-like antiepileptic, herbicide agents (2) and patented, for examples as therapeutic agents for liver disorders (3). As a part of our program on the reactivity of heterocycles, we are now interested in the study of the reactivity of 2,4-piperidinedione-3-carboxylic acid ester.

Methyl N-Benzyl-β-alaninate **1** was obtained admixed with the tertiary amine **2** by Michael addition of methyl acrylate on benzylamine (52:38% yield respectively) in a mixture of methanol, water and triethylamine, according the procedure of Christie and Rapoport (4). Finally, **1** was obtained in 86% yield in ethanol according the procedure of Huizenga and Pandit (5). Compound **1** reacts with methyl malonyl chloride in dichloromethane-water in presence of potassium carbonate to give the amide **3** with 92% yield (6). The ^{1}H and ^{13}C-NMR spectra were more complex due to the presence of two rotamers in the 60:40 ratio. In the case of acyclic amide, it was well established that the groupment in trans from the carbonyl resonate at a lower field

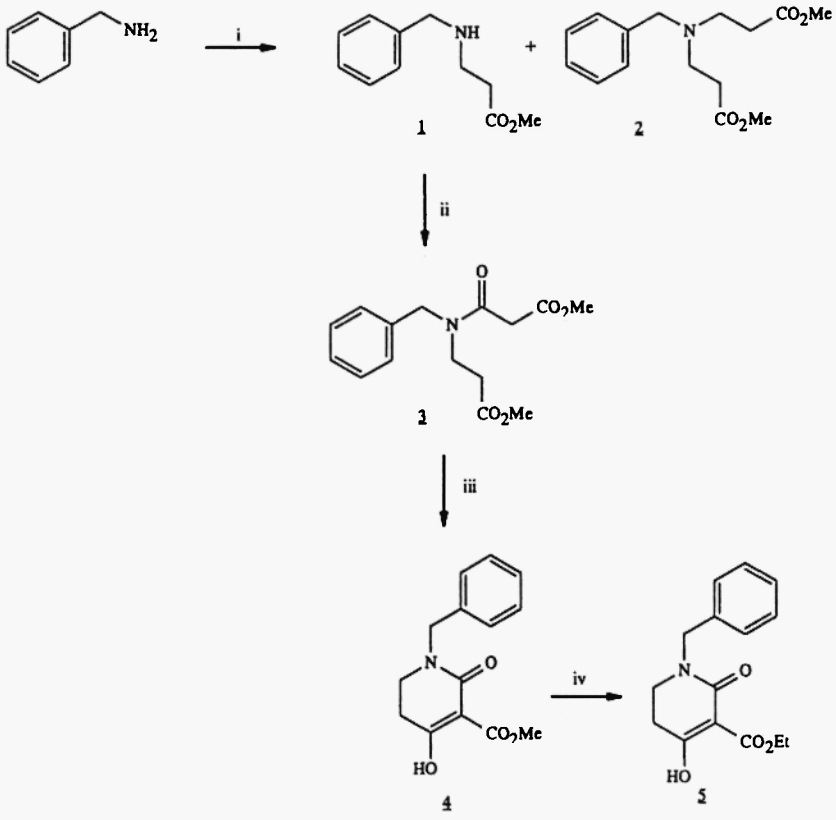
than the cis (7). These results, in good agreement with the anisotropy diamagnetic model of amide described by Paulsen and Todt (8) led to the following assignments.



60% 40%

The total proton and carbon attribution for minor and major rotamers was made using ^{1}H-^{1}H COSY and ^{1}H-^{13}C HETCOR (see experimental section).

The Dieckmann cyclisation of 3 with sodium methylate in refluxing benzene occurred regiospecifically to give methyl 1-benzyl-4-hydroxy-5,6-dihydropyridin-2-one-3-carboxylate 4 in 62% yield (6).



Reagents and conditions: i: methyl acrylate, H_2O, MeOH, Et_3N, 5 h 0°C or methyl acrylate, EtOH, 2 h room temperature, then 30 min reflux; ii: $ClCOCH_2CO_2Me$, CH_2Cl_2, K_2CO_3 (15% in water), 30 min 10°C then 3 h room temperature; iii: MeONa, C_6H_6, 6 h reflux; iv: EtOH, CH_2Cl_2, 48 h, room temperature.

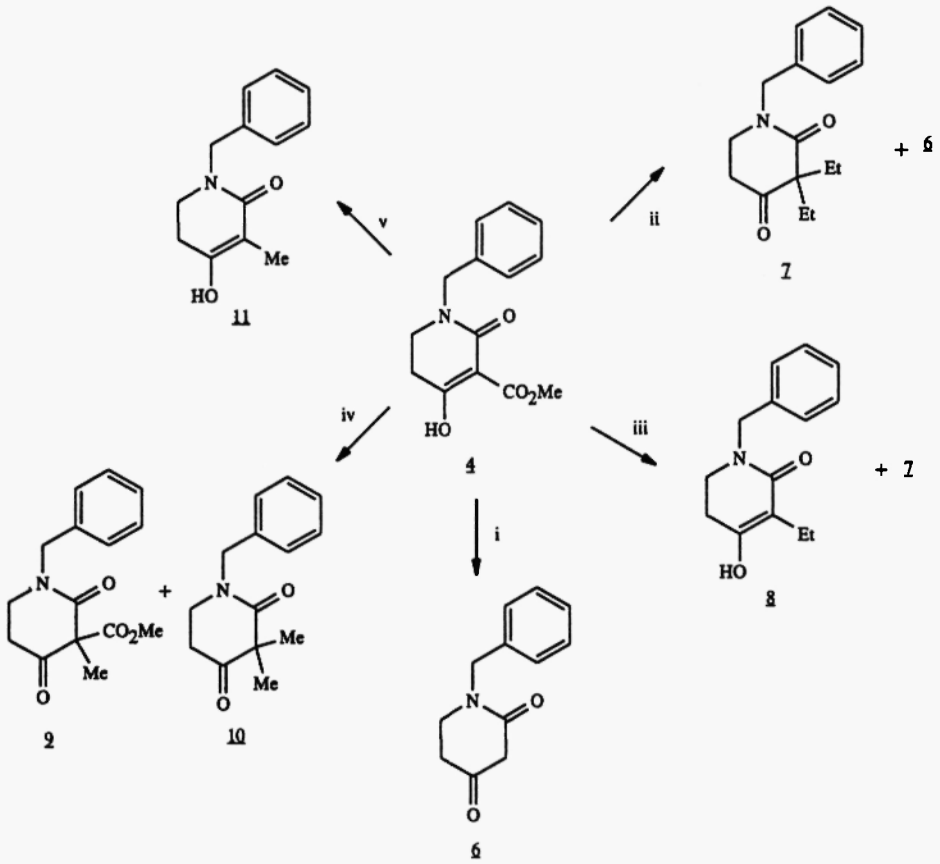
The ^{1}H-NMR spectra showed that this compound appeared in the enol form with a broad singlet at 13.9 ppm. This result was ascertained by ^{13}C-NMR using XHCOR and LRCOR experiments. The derivative 4 was shown to be unstable and was stored at +4°C in dichloromethane. Surprisingly after two weeks the formation of a second product was found. Separation and structural determination showed that transesterification with ethanol (used as dichloromethane stabilizer) had occurred to give 5.

Next the reactivity of the enol 4 was investigated. Thus decarbomethoxylation in refluxing 10% sulfuric acid according to the procedure of Kline (9) gave 1-benzyl-2,4-piperidinedione 6 in 52% yield (10). The structure was determined by ^{1}H-NMR spectroscopy with two triplets at δ: 2.51 and 3.42 (H-5 and H-6) and a singlet for H-3 (δ: 3.40). Further confirmation was done by ^{13}C-NMR and mass spectroscopy with a *m/z* at 203 (100%).

We were then interested in the preparation of some 3-alkyl derivatives. In this way, reaction of 4 with alkyl iodides was investigated. The alkylation of ethyl 1-benzyl-2,5-dioxopiperidine-4-carboxylate with alkyl halide in refluxing acetone in the presence of potassium carbonate has been reported by Bonjoch (11), while stereoselectivity of this method at room temperature has been recently reported by Prakash Rao (12). In refluxing acetone, ethyl iodide gave a mixture of two compounds. The first was determined as the β-ketoamide 6 by comparison with spectral data described before. The ^{1}H-NMR spectral data at 250 MHz of 7 showed the disappearance of the methoxy resonance and the presence of two ethyl groups with a triplet at δ: 0.76 (6H) and two quadruplets at δ: 1.89 (2H) and δ: 1.91 (2H) consistent with the 1-benzyl-3,3-diethyl-2,4-piperidinedione structure. Further confirmations were obtained by ^{13}C-NMR spectroscopy with a δ: 62.8 for C-3 and a ketone absorption at δ: 203.9 and by mass spectroscopy with a *m/z* at 259. The reaction of 4 with ethyl iodide occured smoothly at room temperature to give the diethyl derivative 7 admixed with 1-benzyl-4-hydroxy-3-ethyl-5,6-dihydropyridin-2-one 8 in 45% yield. The structure was elucidated from ^{1}H-nmr spectra and mass spectroscopy (see experimental section). Methyl iodide in refluxing acetone gave a set of two compounds. The first (52.5%) was determinated as 1-benzyl-3,3-dimethyl-2,4-

piperidinedione 10 in particular with a quaternary carbon at δ: 64.7 for C-3. Compound 9, obtained in 8% yield, was identified as methyl 1-benzyl-3-methyl-2,4-piperidinedione-3-carboxylate. Proofs of the structure was found in ^{13}C-NMR spectrum with a CH_3 absorption at δ: 17.9 and a methoxy group at δ: 53.2. When the reaction was run at room temperature, compound 10 was obtained admixed with 1-benzyl-4-hydroxy-3-methyl-5,6-dihydropyridine-2-one 11 (30%). The structure was ascertained by ^{1}H-NMR spectrum with a methyl group as a singlet at δ: 1.35 and an enolic hydrogen at δ 5.10 ppm.

Decarbomethoxylation at room temperature in acetone/potassium carbonate led to partial degradation while only traces of ketoamide 6 may be visualized by tlc. From these results it appeared that alkylation at room temperature occurred principally before decarbomethoxylation while the order of the reaction seemed reversed in refluxing acetone.



Reagents and conditions: i: H_2SO_4 10% reflux; ii: EtI, K_2CO_3, acetone, 5 h, reflux; iii: EtI, K_2CO_3, acetone, 6 h, room temperature; iv: MeI, K_2CO_3, acetone, 5 h, reflux; v: MeI, K_2CO_3, acetone, 5 h, room temperature.

Experimental Part

General information

^{1}H-NMR spectra were recorded on Bruker AC 100, AC 250, WM 360 or AM 400 WB. ^{13}C-NMR are performed on a Bruker AC 100 (25 MHz) or Bruker AM 400 WB (100 MHz). Chemical shift are reported in ppm from TMS with the resonance of the residual $CHCl_3$ (7.27 ppm) or from the center resonance of $CDCl_3$ (77.10 ppm). Mass spectra were recorded on a LKB 2091 (EI) or JEOL JMS DX300 (FAB$^+$). Solvents and reagents were dried prior to used. Thin layer chromatography were performed on Merck 0.25 precoated silica gel ^{60}F254 plates. Acetone was of pure grade and anhydrous. All compounds used in this work were purchased from Aldrich at the pure grade level. All reactions were carried out under a flux of dry nitrogen or argon. All new compounds gave satisfactory elemental analyses.

Methyl N-benzyl-β-alaninate **1** *and N,N-bis(methoxycarbonylethyl)-benzylamine* **2**:

Method A: To a cooled solution (0°C) of benzylamine (30 g, 0.279 mol) in 180 ml of water, 90 ml of methanol and 40 ml of triethylamine, was slowly added methyl acrylate (25.2 ml, 0.279 mol). The mixture was stirred for 5 hours at 0°C. Dichloromethane was added and organic layer was collected, dried over calcium chloride and concentrated under reduced pressure. The residual oil was chromatographed on silica gel eluted with ether to give 15.1 g of **2** (38%) as pale yellow oil; ^{1}H-NMR ($CDCl_3$, 250 MHz), δ: 2.45 (t, 4H, J = 7.1, 2H-2+2H-2'); 2.78 (t, 4H, J = 7.1, 2H-3+2H-3'); 3.57 (s, 2H, CH_2-Ar); 3.62 (s, 6H, 2OCH_3); 7.29 (m, 5H, 5Hphenyl). ^{13}C-NMR ($CDCl_3$, 25 MHz), δ: 32.3 (C-2, C-2'); 48.9 (C-3, C-3'); 51.2 (OCH_3); 58.1 (CH_2-Ar); 126.8 (C-4'); 127.9 (C-3',5'); 128.4 (C-2',6'); 138.8 (C-1'); 172.5 (C=O). Further elution gave 27.9 g of **1** (52%) as pale yellow oil; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 1.78 (br.s., 1H, NH); 2.53 (t, 2H, J = 6.4, 2H-2); 2.89 (t, 2H, J = 6.4, 2H-3); 3.66 (s, 3H, OCH_3); 3.79 (s, 2H, CH_2-Ar); 7.31 (m, 5H, 5Hphenyl). ^{13}C-NMR ($CDCl_3$, 100 MHz), δ: 34.4 (C-2); 44.4 (C-3); 51.5 (OCH_3); 53.6 (CH_2-Ar); 126.9 (C-4'); 128.0 (C-3',5'); 128.3 (C-2',6'); 140.7 (C-1'); 173.1 (C=O). MS (EI) m/z (%): 193 (M+, 5), 192 (10).

Method B: A solution of methyl acrylate (2.15 g, 25 mmol) in 30 ml of dry ethanol was added to benzylamine (2.67 g, 25 mmol) in 50 ml of ethanol. The mixture was stirred for 2 h at room temperature, then refluxed for 30 minutes. After cooling, the solution was concentrated, evaporated, the residue chromatographed on silica gel and eluted with ether to give the amine **1** as pale yellow oil in 86% yield.

N-benzyl-N-carbomethoxyethyl methyl malonamide **3**: To a solution of **1** (500 mg, 2.5 mmol) in 5 ml of dichloromethane and 4 ml of a 15% potassium carbonate solution cooled to 10°C was added methyl malonyl chloride (378 mg, 2.77 mmol) in dichloromethane (5 mL). The mixture was stirred at 10°C for 30 min allowed to stand at room temperature and stirred for 3 h. The organic layer was collected and aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over calcium chloride and evaporated to dryness. The residue was chromatographed on silica gel eluted with dichloromethane to give 670 mg (92%) of **3** as a mixture of two rotamers; ^{1}H-NMR ($CDCl_3$, 400 MHz), δ: 2.52 (t, 2H, J = 7, 2H-2 min); 2.62 (t, 2H, J = 6.9, 2H-2 maj); 3.42 (s, 2H, 2H-2' maj); 3.52 (t, 2H, J = 7, 2H-3 min); 3.61 (t, 2H, 2H-3 maj); 3.61 (s, 3H, OCH_3 maj); 3.62 (s, 3H, OCH_3 min); 3.63 (s, 2H, 2H-2' min); 3.67 (s, 3H, OCH_3 maj); 3.73 (s, 3H, OCH_3 min); 4.57 (s, 2H, CH_2-Ar maj); 4.60 (s, 2H, CH_2-Ar min); 7.26 (m, 5H, 5Hphenyl min+maj). ^{13}C-NMR ($CDCl_3$, 100 MHz), δ: 32.2 (C-2, min); 32.8 (C-2 maj); 40.8 (C-2', min); 41.1 (C-2', maj); 43.0 (C-3, min); 43.1 (C-3,

maj); 47.9 (C-1", min); 51.7 (OCH_3, maj); 51.9 (OCH_3, min); 52.7 (C-1", maj); 52.8 (OCH_3, min+maj); 126.3 (C-4phenyl min+maj); 127.5 (C-3,5phenyl min); 127.8 (C-3,5phenyl, maj); 128.6 (C-2,6phenyl, min); 129.0 (C-2,6phenyl maj); 136.1 (C-1phenyl, min); 136.7 (C-1phenyl, maj); 166.4 (CO min); 166.6 (CO maj); 167.8 (CO maj); 168.0 (CO min); 171.3 (CO min); 172.3 (CO maj). MS (EI) m/z (%): 293 (M+, 45), 191 (100

Methyl 1-benzyl-4-hydroxy-5,6-dihydropyridin-2-one-3-carboxylate 4: To a solution of sodium methylate (from sodium (30 mg, 1.7 mat. g.) in 2 ml of methanol) was added under nitrogen a solution of 3 (500 mg, 1.73 mmol) in 5 ml of benzene. The mixture was refluxed for 6 h. After cooling the solution was treated with water and the two layers were separated. The aqueous layer was acidified to pH=1 and extracted with dichloromethane. After drying and evaporation, the residue was chromatographed on silica gel eluted with dichloromethane to give 140 mg (62%) of 4. ^{1}HNMR ($CDCl_3$, 360 MHz), δ: 2.57 (t, 2H, J = 6.9, 2H-5); 3.32 (t, 2H, J = 6.9, 2H-6); 3.91 (s, 3H, OCH_3); 4.62 (s, 2H, CH_2-Ar); 7.27 (m, 5H, 5Hphenyl); 13.90 (br.s, 1H, OH). ^{13}C-NMR ($CDCl_3$, 90 MHz), δ: 29.5 (C-5); 41.6 (C-6); 49.5 (CH_2-Ar); 52.4 (OCH_3); 98.0 (C-3); 127.8 (C-4phenyl); 128.0 (C-3,5phenyl); 128.6 (C-2,6phenyl); 162.2 (COamide); 172.3 (COester); 182.4 (C-4). MS (EI) m/z (%): 262 ($M^{+\cdot}$,8), 229 (24), 91 (100).

Ethyl 1-benzyl-4-hydroxy-5,6-dihydropyridin-2-one-3-carboxylate 5: This compound was isolated by chromatography on silica gel eluted with dichloromethane; ^{1}H-NMR ($CDCl_3$, 250 MHz), δ: 1.43 (t, 3H, J = 7.1, CH_3); 2.57 (t, 2H, J = 6.8, 2H-5); 3.32 (t, 2H, J = 6.8, 2H-6); 4.40 (q, 2H, J = 7.1, CH_2); 4.65 (s, 2H, CH_2-Ar); 7.28 (m, 5H, 5Hphenyl); 14.05 (br.s, 1H, OH).

1-Benzyl-2,4-piperidinedione 6: A solution of 4 (2 g, 7.63 mmol) in 40 ml of a 10% sulfuric acid solution was refluxed for 10 hours. After cooling, ice water was added and the solution made basic with potassium carbonate. Extraction with ether then dichloromethane and usual work up gave a residual oil which was chromatographed on silica gel. Elution with dichloromethane gave 800 mg (52%) of 6 which crystallized on standing; m.p. 164-165° [Lit. (10) 165-166°]. ^{1}H-NMR ($CDCl_3$, 360 MHz), δ: 2.51 (t, 2H, J = 6.2, 2H-5); 3.40 (s, 2H, 2H-3); 3.42 (t, 2H, J = 6.2, 2H-6); 4.66 (s, 2H, CH_2-Ar); 7.30 (m, 5H, 5Hphenyl). ^{13}C-NMR ($CDCl_3$, 90 MHz), δ: 38.6 (C-5); 42.3 (C-6); 48.8 (C-3); 49.6 (CH_2-Ar); 127.3 (C-4phenyl); 127.9 (C-3,5phenyl); 128.8 (C-2,6phenyl); 136.2 (C-1phenyl); 166.2 (C=Oamide); 203.2 (C=Oketone). MS (EI) m/z (%): 203 (M+.,100).

1-Benzyl-3,3-diethyl-2,4-piperidinedione 7: To a mixture of 4 (1 g, 3.8 mmol), potassium carbonate (870 mg, 7.6 mmol) in 20 ml of acetone was added ethyl iodide (4.9 g, 38 mmol). The suspension was refluxed for 5 h. After cooling, the crude material was filtered, washed with acetone, and the solvent removed under reduced pressure. The residue was disolved in dichloromethane, the solution was washed with water, brine, dried over calcium chloride and concentrated. The residue was chromatographed on silica gel by elution with dichloromethane to give 7 (40%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$, 250 MHz), δ: 0.76 (t, 6H, J = 7.5, CH_3); 1.89 (q, 2H, J = 7.5, CH_2); 1.91 (q, 2H, J = 7.5, CH_2); 2.56 (t, 2H, J = 6.5, 2H-5); 3.36 (t, 2H, J = 6.5, 2H-6); 4.72 (s, 2H, CH_2-Ar); 7.30 (m, 5H, 5Hphenyl). ^{13}C-NMR ($CDCl_3$, 25 MHz), δ: 9.9 (CH_3); 31.2 (CH_2); 40.4 (C-5*); 41.2 (C-6*), 50.8 (CH_2-Ar); 62.8 (C-3); 127.8 (C-4phenyl); 128.3 (C-3,5phenyl); 128.9 (C-2,6phenyl); 136.8 (C-1phenyl); 172.3 (COamide); 203.9 (COketone). MS

(EI) m/z (%): 259 (M+.,33), 231 (100), 216 (80). Further elution gave 6 (154 mg, 20%).

1-Benzyl-4-hydroxy-3-ethyl-5,6-dihydropyridin-2-one 8 and 1-benzyl-3,3-diethyl-2,4-piperidinedione 7: To a solution of enol 4 (1 g, 3.8 mmol) in 20 ml of acetone was added ethyl iodide (4,9 g, 38 mmol) in 20 ml of acetone and potassium carbonate (0.87 g, 7.6 mmol). The suspension was stirred at room temperature for 6 h then filtered. The precipitate was washed with acetone and the organic layer concentrated. Work up as above give 7 (147 mg, 15%). Further elution gave 393 mg of 8 (45%) as pale yellow oil. ^{1}H-NMR ($CDCl_3$, 250 MHz), δ: 1.30 (t, 3H, J = 7, CH_3 ethyl); 2.35 (t, 2H, J = 7,1, 2H-5), 3.25 (t, 2H, J = 7,1, 2H-6); 3.85 (q, 2H, J = 7, CH_2 ethyl); 4.55 (s, 2H, CH_2-Ar); 5.10 (s, 1H, OHenol); 7.20 (m, 5H, 5Hphenyl). MS (EI) m/z (%): 230 ($M^{+\cdot}$, 12).

Methyl 1-benzyl-3-methyl-2,4-piperidinedione-3-carboxylate 9 and 1-benzyl-3,3-dimethyl-2,4-piperidinedione 10: The same procedure using methyl iodide (38 mmol) in refluxing acetone gave 10 (546 mg, 52.5%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$, 100 MHz), δ: 1.37 (s, 6H, $2CH_3$); 2.62 (t, 2H, J = 6.3, 2H-5); 3.39 (t, 2H, J = 6.3, 2H-6); 4.66 (s, 2H, CH_2-Ar); 7,27 (m, 5H, 5Hphenyl). ^{13}C-NMR ($CDCl_3$, 25 MHz), δ: 22.8 (CH_3); 37.0 (C-5); 41.5 (C-6); 50,8 (CH_2-Ar); 52.9 (C-3); 127.8 (C-4phenyl); 128.0 (C-3,5phenyl); 128.8 (C-2,6phenyl); 136.6 (C-1phenyl); 173.1 (C=Oamide); 208.9 (C=Oketone). Anal. calc. for $C_{14}H_{17}NO_2$: C 72.70, H 7.41, N 6.06; found: C 72.82, H 7.36, N 5.95. Further elution gave 85 mg of 9 (8%) as pale yellow oil. ^{1}H-NMR ($CDCl_3$, 250 MHz), δ: 1.62 (s, 3H, CH_3), 2.75 (m, 2H, 2H-5); 3.45 (m, 2H, 2H-6); 3,75 (s, 3H, OCH_3); 4.6 (d, 1H, J = 14.7, CH_2-Ar); 4.8 (d, 1H, J = 14.7, CH_2-Ar); 7,3 (m, 5H, 5Hphenyl); ^{13}C NMR ($CDCl_3$, 25 MHz), δ: 17.9 (CH_3); 37.3 (C-5); 41,4 (C-6); 51.0 (CH_2-Ar); 53.2 (OCH_3); 64.7 (C-3); 127.9 (C-3,4,5phenyl); 128.8 (C-2,6); 136.0 (C-1phenyl); 167.2 (C=Oester*); 167.8 (C=Oamide*); 202.1 (C=Oketone).

1-Benzyl-4-hydroxy-3-methyl-5,6-dihydropyridin-2-one 11 and 1-benzyl-3,3-dimethyl-2,4-piperidinedione 10: The same procedure at room temperature gave 417 mg of 10 (40%) as a pale yellow oil. Further elution gave 246 mg of 11 (30%); ^{1}H-NMR ($CDCl_3$, 250 MHz), δ: 1.35 (s, 3H, CH_3); 2.35 (t, 2H, J = 7,1, 2H-5); 3.25 (t, 2H, J = 7,1, 2H-6); 4.55 (s, 2H, CH_2-Ar); 5.10 (br. s., 1H, OH); 7.20 (m, 5H, Hphenyl).

Acknowledgments

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References

(1) M. Rubiralta, E. Giralt, A. Diez, in "Piperidine: Structure, Preparation, Reactivity and synthetic applications of piperidine and its derivatives", Ed. Elsevier, Amsterdam, 1991, pp. 313-434.

(2) S. Sugasawa, T. Fujii, Pharm. Bull. (Japan), 3, 47, (1955); Y. Ban, Pharm. Bull. (Japan), 3, 53, (1955); M. Barasch, J.M. Osbond, J.C. Wickens, J. Chem. Soc., 3530 (1959); E. Masset, U.S. Patent, 2,525,231, (1950) (Chem. Abstr., 3426a, (1951)); N.J. Geach, J. Gilmour, L.R. Halton, P.H.G. Smith, Eur. Pat. Appl. 278,742 (1988) (Chem. Abstr., 110, 38898b, (1989)).

(3) I. Iijima, K. Hanma, Y. Saiga, Y. Matsukoa, M. Matsumoto, Jpn. Kokai Tokkyo Koho (Chem. Abstr., 108, 37653q, (1987)).

(4) B.D. Christie, H. Rapoport, J. Org. Chem., 50(8), 1239, (1985).

(5) R.H. Huizenga, U.K. Pandit, Tetrahedron, 47(24), 4155, (1991).

(6) A.G. Schultz, R.D. Lucci, J.J. Naper, H. Kinoshita, R. Ravivhandian, P. Shannon, Y.K. Yee, J. Org. Chem., 50(2), 217, (1985). This compound was reported but without experimental procedure, physical and spectral properties.

(7) W.E. Steward, T.H. Siddall III, Chem. Rev., 70, 517, (1970).

(8) H. Paulsen, K. Todt, Angew. Chem. Int. Ed., 5, 829, (1966).

(9) G.B. Kline, J. Am. Chem. Soc., 81, 2251, (1959).

(10) S. Takano, K. Yuta, S. Hatakeyama, K. Ogasawara, Tetrahedron Lett., 4, 369, (1979). This compound was reported without experimental procedure and spectral properties.

(11) J. Bonjoch, I. Serret, J. Bosch, Tetrahedron, 40(13), 2505, (1984).

(12) H.S. Prakash Rao, K. Subba Reddy, S.N. Balasubrahmanyam, Tetrahedron Lett., 35(11), 1759, (1994).

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