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SYNTHESIS OF 2,5-PIPERIDINEDIONES. REGIOSELECTIVITY IN THE DIECKMANN CYCLIZATION[1]

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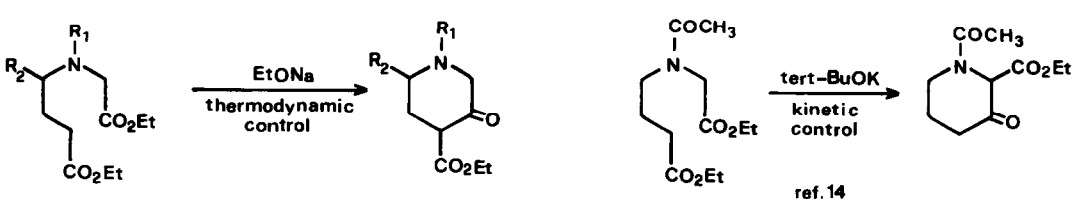
Abstract - Dieckmann cyclization of ethyl *N*-benzyl-*N*-[(ethoxycarbonyl)methyl]succinamate (2) with sodium ethoxide gave regioselectively β-keto ester 3, whereas when using potassium *tert*-butoxide or potassium hydride as a base the regioisomer 4 was isolated as the main product. Transesterification of ethyl β-keto esters 3 and 4 with benzyl alcohol followed by hydrogenolysis and decarboxylation of the resulting benzyl esters 5 and 6 led to 1-benzyl-2,5-piperidinedione (1). The preparation of some 4-alkyl- and 4-alkoxycarbonylalkyl derivatives was achieved by alkylation of 5 with the appropriate halide and further hydrogenolysis.

3-Piperidones have been used as synthetic intermediates,[2,3] specially in the synthesis of alkaloids[4] and compounds with pharmacological interest.[5] However little work has been reported on the preparation and synthetic applications of 2,5-piperidinediones.[6,7]

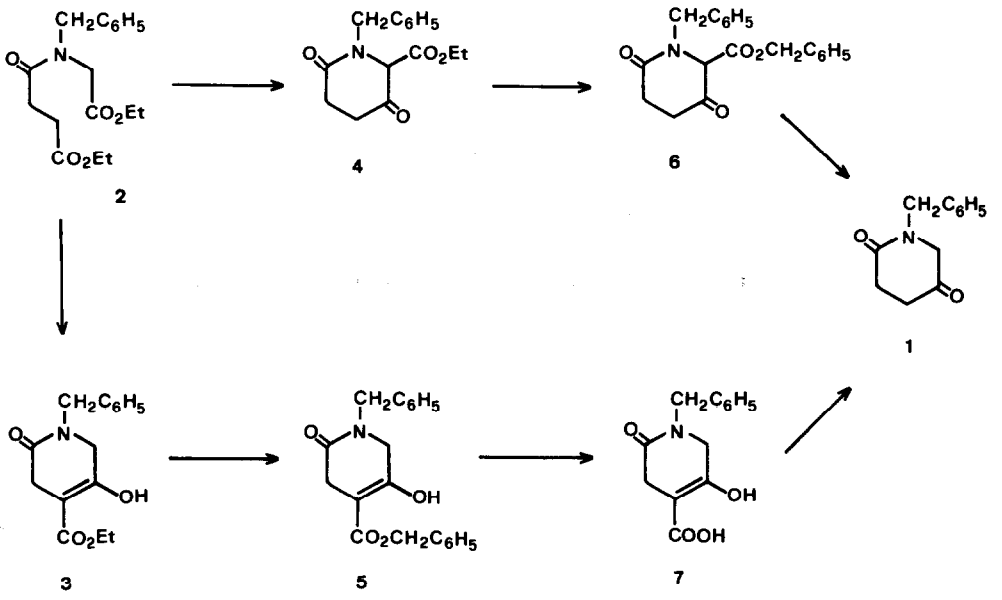
Continuing our interest on functionalized piperidines as starting materials for the synthesis of bridged azabicyclic systems,[8] the purpose of the present work was the preparation of the hitherto unknow 1-benzyl-2,5-piperidinedione (1) and some 4-substituted derivatives by Dieckmann cyclization of an appropriate amido diester.

It is well know that Dieckmann cyclization[9] is regioselective when one of the two ester groups has a methine α-carbon or when, in the presence of an appropriate base, the acidity of the two α-methylene groups or the stability of the two possible cyclized products is different.[10] This has been applied to the preparation of 3-piperidones. Thus, the regioselective formation of 4-ethoxycarbonyl-3-piperidones by cyclization of unsymmetrical amino-[11,12] or amido diesters[13] under thermodynamic control conditions as well as that of 2-ethoxycarbonyl-3-piperidones by cyclization of unsymmetrical *N*-acylamino diesters[14,15] under kinetic control conditions has been reported. However, to our knowledge there are no examples in the piperidine



ref. 14

$R_1 = CH_3$ $R_2 = H$ ref. 11
$R_1 = CH_2C_6H_5$ $R_2 = H$ ref. 12
$R_1 = COC_6H_5$ $R_2 = CO_2Et$ ref. 13



series[16] for product control leading to both possible isomeric keto esters *via* Dieckmann condensation from the same unsymmetrical α-unsubstituted diester.

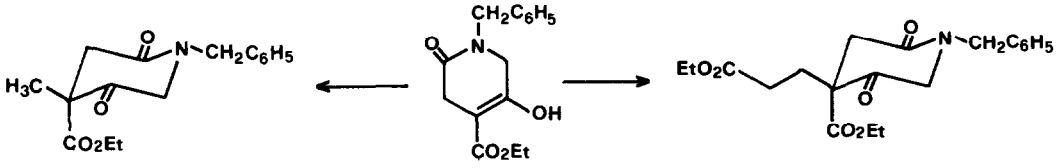
Dieckmann cyclization of amido diester 2 constitutes an example in which that product control has been achieved. Amido diester 2 was prepared by condensation of ethyl *N*-benzylglycinate[17] with ethyl 3-chloroformylpropionate[18] in the presence of potassium carbonate. Treatment of 2 with sodium ethoxide in dioxane,[19] followed by a cautious work-up,[20] afforded keto ester 3 in excellent yield (80%), whereas under non-equilibrating conditions (potassium *tert*-butoxide, toluene) the regioisomer 4 was isolated as the main product (ratio 4/3 = 3:2, 84% overall yield). Using potassium hydride as a base in THF the ratio was 6:1, but the yield decreased to 60%. In fact, we expected that a rate-determined condensation would favour formation of 4 owing to the predictable higher acidity of the methylene protons adjacent to the nitrogen atom. As could be expected, when keto ester 4 was subjected to equilibrating conditions (sodium ethoxide in refluxing ethanol) it was converted into 3, the most stable of the two regioisomeric keto esters.

It is worth commenting upon the different tautomeric behavior of keto esters 3 and 4. By ^{1}H-NMR and IR spectroscopy the former was shown to be almost exclusively in the enol form, whereas the latter appeared to be in the keto form. Thus, 3 showed an infrared absorption at 1680 cm^{-1} attributed to the enol ester, which was absent in 4, and a NMR singlet at δ12.30 due to the enolic proton. On the other hand, the methylene protons at positions 3 and 6 show an homoallylic coupling (J= 3 Hz) due to the presence of the enolic C_4-C_5 double bond. On the contrary, in the NMR spectrum of 4 the methine proton of the β-keto ester moiety resonates as a singlet at δ4.30. The predominance of the keto form in 4, unusual in β-keto esters in six membered cyclic systems,[21] can be accounted for by considering that the steric crowding between ethoxycarbonyl and *N*-benzyl groups are greater in the enol tautomer than in the keto form due to the sp^2 character of C-2.

The direct decarbethoxylation of ethyl β-keto esters 3 and 4 by hydrolysis in acidic conditions or by heating in DMSO in the presence of lithium chloride occurred in low yield, and abundant loss of material and product decomposition was observed. However, 3 was satisfactorily converted into 2,5-piperidinedione 1 by a two-step sequence, consisting in transesterification with benzyl alcohol[22] followed by hydrogenolysis of the resulting benzyl ester 5 and thermal decarboxylation of the intermediate β-keto acid 7. Similarly, ethyl β-keto ester 4 furnished

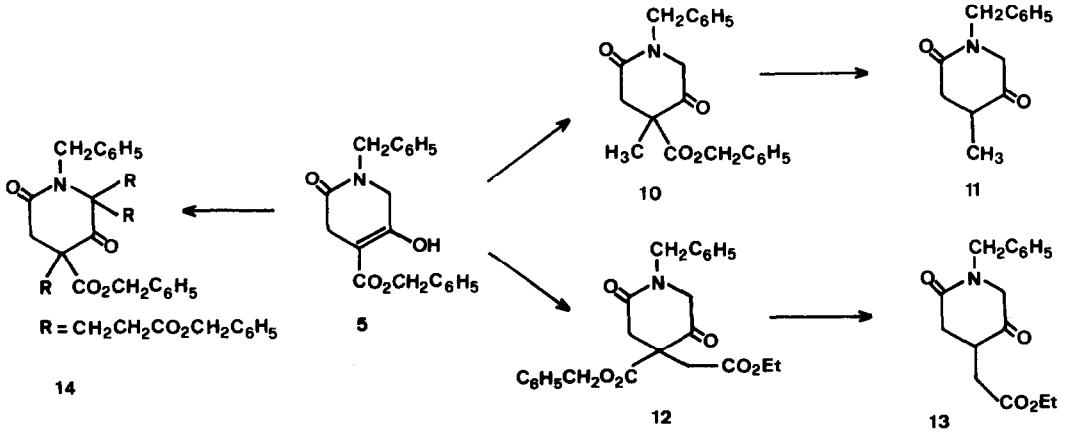
1 through the corresponding benzyl ester 6. In this case the intermediate β-keto acid could not be isolated. As in the above ethyl series, β-keto ester 5 appeared to be enolic, unlike 2-substituted isomer 6. Piperidinedione 1 showed two intense absorptions at 1735 and 1660 cm^{-1} in its IR spectrum, corresponding to ketone and lactam carbonyl groups. In the NMR spectrum, singlets at δ2.65, 3.70, 4.50, and 7.15, due to 3- and 4-methylene,6-methylene, benzylic, and aromatic protons, respectively, were observed.

Having obtained piperidinedione 1, we then proposed preparing some 4-alkyl- and 4-alkoxycarbonylalkyl substituted derivatives. The former (i.e.11), as well as the parent compound 1, can be envisaged as potential intermediates for the synthesis of functionalized 2-azabicyclo[3.3.1]nonanes[23,24] *via* an α,α'-annelation reaction such as it has been reported for the carbocyclic series.[25] Similarly, 2,5-piperidinediones with an alkyl propionate substituent at the 4-position could be further elaborated to functionalized 2-azabicyclo[3.3.1]nonanes in a way similar to that previously reported starting from 3-oxo-2-piperidinepropionic acid derivatives.[8b,c] Finally, 4-ethoxycarbonylmethyl substituted derivatives (i.e.13) could represent a new synthetic entry to alkaloids bearing a 4-piperidineacetate moiety.



8 3 9

Alkylation of β-keto ester 3 with methyl iodide or ethyl 3-bromopropionate in acetone solution in the presence of anhydrous potassium carbonate led in good yields to piperidines 8 and 9, respectively. However, the decarbethoxylation of these ethyl β-keto esters in acidic media under usual reaction conditions failed. By this reason, we turned our attention to the alkylation of benzyl β-keto ester 5. Alkylation of 5 with methyl iodide furnished 10 which, by hydrogenolysis in the presence of palladium on charcoal and further decarboxylation, was converted into 4-methyl-2,5-piperidinedione 11. Similarly, alkylation of 5 with ethyl bromoacetate using THF as a solvent[26] followed by hydrogenolysis of the resulting diester



14 5 10 11 12 13

12 gave the expected 4-piperidineacetate 13. In contrast to the above alkylations, attempts to introduce a benzyl propionate side chain into 5 were unsuccessful. Thus, alkylation of β-keto ester 5 with benzyl 3-bromopropionate using potassium carbonate as a base required prolonged reaction times, as was evident from the ferric chloride test, and the polyalkylated piperidine 14 was isolated as the main product.

Some NMR spectral features of piperidinediones 8-13 prepared in this work are worthy of comment since they can be indicative of their conformational behavior. Thus, in compounds 10, 11, and 13 the *N*-benzyl methylene protons appear as a singlet whereas in the piperidinediones 8, 9, and 12 these protons give rise to an AB quartet. In these cases, the observed magnetic non-equivalence could be accounted for by considering that in the preferred conformation there is an axial alkoxycarbonyl substituent at the 4-position of the piperidine ring.

EXPERIMENTAL

General. ^{1}H-NMR spectra were recorded in $CDCl_3$ with TMS as internal standard (60 MHz: Perkin-Elmer R-24B; 200 MHz: Varian XL-200). ^{13}C-NMR spectrum was determined on a Varian XL-200 spectrometer. Chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were taken with a Perkin-Elmer 577 spectrophotometer, and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were obtained with a Hewlett-Packard 5930 A spectrometer. Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. Column and thin-layer chromatography were done by using silica gel 60 (Merck). Iodoplatinate reagent was used to locate the reaction components. Microanalyses were performed by the Instituto de Química Orgánica, Barcelona.

Ethyl N-Benzyl-N-[(ethoxycarbonyl)methyl]succinamate (2). A solution of ethyl 3-chloroformylpropionate[16] (41.1 g, 0.25 mol) in anhydrous benzene (350 ml) was added dropwise at 10°C for 30 min to a stirred mixture of ethyl *N*-benzylglycinate[17] (38.6 g, 0.2 mol), benzene (350 ml), and 15% aqueous potassium carbonate solution (260 ml, 0.28 mol). The resulting mixture was allowed to warm to room temperature, adjusted to pH 11-12 with 15% aqueous potassium carbonate solution, and stirred at room temperature overnight. The benzene layer was separated and washed with 10% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and water. Drying and evaporation of the solvent gave 55 g (85%) of 2 as an oil which was used without further purification. An analytical sample was obtained by distillation, b. p. 220-230°C/0.2 mm[27]; NMR 1.21 (t,6H,$CO_2CH_2CH_3$), 2.5-2.8 (br signal,4H,CH_2), 3.98 (s,2H,NCH_2), 4.13 (q,4H,$CO_2CH_2CH_3$), 4.62 (s,2H,NCH_2Ar), 7.27 (s, 5H,ArH); IR (NaCl), 1740 (ester), 1660 (amide). (Found: C, 63.86; H, 7.26; N, 4.50. Calcd. for $C_{17}H_{23}NO_5$: C, 63.55; H, 7.17; N, 4.36).

Ethyl 1-Benzyl-2,5-dioxo-4-piperidinecarboxylate (3). A solution of 2 (25 g, 78 mmol) in anhydrous dioxane (100 ml) containing 6.8 ml (116 mmol) of dry ethanol was added dropwise under nitrogen to a stirred suspension of sodium dispersion (2.7 g, 117 mmol) in anhydrous dioxane (100 ml). The resulting solution was refluxed for 7 h. After cooling, acetic acid (6.8 ml, 119 mmol) and chloroform (350 ml) were added, and the solution was washed with 10% aqueous sodium dihydrogen phosphate solution (300 ml). The chloroform extracts were washed with pH 7 phosphate buffer, dried, and evaporated. The residue was triturated with ether-acetone to give 3 (17.5 g, 80%) as a yellow solid. A sample recrystallized from acetone-ether melted at 102-104°C; NMR 1.30 (t,3H,$CO_2CH_2CH_3$), 3.20 (t,J=3 Hz,2H,$NCOCH_2$), 3.85 (t,J=3 Hz,2H,NCH_2CO), 4.20 (q,2H,$CO_2CH_2CH_3$), 4.60 (s,2H,NCH_2Ar), 7.30 (s,5H, ArH), 12.30 (s,1H,OH); IR (KBr), 1680 (enol ester), 1640 (amide); MS, m/e (relative intensity) 275 (M^+,15),229(7),202(7),184(6),138(9),114(10),106(12),91(100),65(22), 55(13). (Found: C, 65.65; H, 6.09; N, 5.14. Calcd. for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.81; N, 5.09).

Ethyl 1-Benzyl-3,6-dioxo-2-piperidinecarboxylate (4).

Method A. To a stirred suspension of freshly sublimed potassium *tert*-butoxide (16.2 g, 144 mmol) in anhydrous toluene (120 ml) at 0°C was added under nitrogen a solution of 2 (30 g, 96 mmol) in anhydrous toluene (180 ml) for 1 h 20 min. The mixture was stirred at room temperature for 2 h 45 min and worked-up as above to give a solid (23 g, 84%) which by NMR was found to be a 3:2 mixture of β-keto esters 4 and 3. These compounds were separated after several fractional crystallizations from ether-acetone. The non-enolic β-keto ester 4 was isolated as a white solid, m.p. 55-57°C; NMR 1.18 (t,3H,$CO_2CH_2CH_3$), 2.7 (s,4H,CH_2), 4.06 (q,2H,$CO_2CH_2CH_3$), 4.30 (s,1H,C_2-H), 4.12 and 5.04 (2d,J=15 Hz,1H each,NCH_2Ar), 7.16 (s,5H,ArH); IR (KBr) 1750 (ester), 1730 (ketone), 1660 (amide); MS, m/e (relative intensity) 275 (M^+,8),202(10),184(9),125(5),112(6),106(6),91(100),74(18),65(22),59(17). (Found: C, 65.71; H, 6.16; N, 5.15. Calcd. for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.18; N, 5.09).

Method B. A potassium hydride oil dispersion (50%, 2 g, 25 mmol) was suspended in anhydrous THF (70 ml) under nitrogen, and a solution of amido diester 2 (7 g, 22 mmol) in anhydrous THF (80 ml) was added dropwise with stirring at room temperature for 15 min. After additional 20 min, the mixture was acidified with acetic acid, diluted with water, and extracted with ether. The material obtained after drying and evaporation of solvent was maintained at 60-70°C/0.5 mm for 2 h. Trituration of the residue in ether afforded 3.5 g (60%) of a solid which by NMR was found to be a 6:1 mixture of β-keto esters 4 and 3.

Reaction of 4 with sodium ethoxide. To a solution of 3.5 ml of absolute ethanol and 150 mg of sodium were added 1.8 g (6.5 mmol) of β-keto ester 4 dissolved in 6 ml of ethanol, and the mixture was heated under reflux for 5 h 30 min. Working up[28] gave 715 mg (40%) of β-keto ester 3 and 626 mg (30%) of 2.

Benzyl 1-Benzyl-2,5-dioxo-4-piperidinecarboxylate (5). A solution of ester 3 (10.5 g, 38 mmol) in benzyl alcohol (19.8 ml, 0.19 mmol) was heated at 170°C in an oil bath for 6 h. The residue after evaporation of benzyl alcohol was crystallized by the addition of ether. Filtration and washing with ether gave 9.5 g (74%) of 5. An analytical sample was obtained by recrystallization from acetone-ether, m.p. 118-120°C; NMR 3.28 (t,J=3 Hz,2H,$NCOCH_2$), 3.85 (t,J=3 Hz,2H,NCH_2CO), 4.60 (s,2H, NCH_2Ar), 5.20 (s,2H,CO_2CH_2Ar), 7.23 and 7.30 (2s,5H each,ArH), 12.20 (s,1H,OH); IR (KBr), 1685 (enol ester), 1645 (amide). (Found: C, 71.18; H, 5.68; N, 4.43. Calcd. for $C_{20}H_{19}NO_4$: C, 71.21; H, 5.64; N, 4.15).

Benzyl 1-Benzyl-3,6-dioxo-2-piperidinecarboxylate (6). Operating as above, the ester 4 was converted into the benzyl ester 6 in 73% yield. A sample recrystallized from acetone-ether melted at 75-77°C; NMR 2.72 (br signal,4H,CH_2), 4.40 (s, 1H,C_2-H), 4.04 and 5.04 (2d,J=15 Hz,NCH_2Ar), 5.03 (s,2H,CO_2CH_2Ar), 7.20 and 7.28 (2s,5H each,ArH); IR (KBr), 1750 (ester), 1730 (ketone), 1660 (amide). (Found: C, 71.27; H, 5.78; N, 4.23. Calcd. for $C_{20}H_{19}NO_4$: C, 71.21; H, 5.64; N, 4.15).

1-Benzyl-2,5-piperidinedione (1).

Method A: From β-keto ester 5. To a solution of 5 (3 g, 8.8 mmol) in ethyl acetate (115 ml) was added 10% palladium on charcoal (1.25 g). The resulting mixture was hydrogenated at room temperature and atmospheric pressure until the solution had absorbed the required volume of hydrogen. The catalyst was filtered off and the filtrate was evaporated to give *1-benzyl-2,5-dioxo-4-piperidinecarboxylic acid* (7); NMR (DMSO-d_6), 3.20 (t,2H,$NCOCH_2$), 3.82 (t,2H,NCH_2), 4.60 (s,2H,NCH_2Ar), 7.20 (s,5H,ArH). When the above solution was refluxed for 2 h and then evaporated, 1.35 g (75%) of ketone 1 was obtained. A sample recrystallized from acetone-ether melted at 67-70°C; NMR 2.65 (s,4H,CH_2), 3.70 (s,2H,NCH_2CO), 4.50 (s,2H,NCH_2Ar), 7.15 (s,5H,ArH); IR (KBr), 1735 (ketone), 1660 (amide). (Found: C, 70.62; H, 6.37; N, 6.74. Calcd. for $C_{12}H_{13}NO_2$: C, 70.93; H, 6.40; N, 6.89).

Method B: From β-keto ester 6. Operating as in the above method A, β-keto ester 6 was converted into 2,5-piperidinedione 1 in 82% yield. In this case, the final warming was unnecessary.

Method C: From β-keto ester 3. Lithium chloride (305 mg, 7.2 mmol), water (65 mg, 3.6 mmol), and DMSO (5 ml) were added to keto ester 3 (1 g, 3.6 mmol). The mixture was heated at 150°C for 3 h 30 min. After the usual work-up[29] 175 mg (24%) of 1 was obtained.

Ethyl 1-Benzyl-4-methyl-2,5-dioxo-4-piperidinecarboxylate (8). A stirred mixture of 3 (1 g, 3.6 mmol), methyl iodide (0.45 ml, 7.2 mmol), and anhydrous potassium carbonate (2 g, 14.4 mmol) in acetone (10 ml) was refluxed for 2 h 30 min. The inorganic materials were filtered and washed with acetone. The evaporation of the combined filtrates gave an oily residue which was dissolved in benzene and washed with water and brine. Evaporation left 8 in nearly quantitative yield. An analytical sample was obtained by recrystallization from ether-acetone, m.p. 99-101°C; NMR: 1.10 (t,3H,$CO_2CH_2CH_3$), 1.35 (s,3H,CH_3), 2.50 and 3.25 (2d,J=17 Hz,1H each,$NCOCH_2$), 3.85 (s,2H,NCH_2CO), 4.05 (q,2H,$CO_2CH_2CH_3$), 4.38 and 4.78 (2d,J=15 Hz, 1H each,NCH_2Ar), 7.25 (s,5H,ArH); IR ($CHCl_3$), 1730 (ketone, ester), 1665 (amide). (Found: C, 66.26; H, 6.64; N, 4.72. Calcd. for $C_{16}H_{19}NO_4$: C, 66.44; H, 6.57; N, 4.85).

Ethyl 1-Benzyl-4-ethoxycarbonyl-2,5-dioxo-4-piperidinepropionate (9). A stirred mixture of 3 (3.5 g, 13.5 mmol), ethyl 3-bromopropionate (13.7 ml, 108 mmol), and anhydrous potassium carbonate (7.45 g, 54 mmol) in acetone (60 ml) was refluxed overnight. The mixture was worked-up as above. After evaporative bulb-to-bulb distillation to remove excess alkylating agent, 9 was isolated (4.37 g, 86%). An analytical sample was obtained by column chromatography (chloroform as eluent); NMR 1.08 and 1.20 (2t,3H each,$CO_2CH_2CH_3$), 1.8-2.5 (m,4H,CH_2), 2.50 and 3.15 (2d,J= 15 Hz,1H each,$NCOCH_2$), 3.78 (s,2H,NCH_2CO), 4.02 and 4.04 (2q,2H each,$CO_2CH_2CH_3$), 4.15 and 4.80 (2d,J=15 Hz,1H each, NCH_2Ar), 7.15 (s,5H,ArH); IR (NaCl), 1730 (ester, ketone), 1660 (amide). (Found: C, 63.74; H, 6.64; N, 3.72. Calcd. for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73).

Benzyl 1-Benzyl-4-methyl-2,5-dioxo-4-piperidinecarboxylate (10). The reaction and work-up of a mixture of 5 (1 g, 2.97 mmol), methyl iodide (0.37 ml, 5.39 mmol), and anhydrous potassium carbonate (1.64 g, 11.88 mmol) in acetone (10 ml) followed those of 3. Evaporation left 1 g (95%) of 10 as a solid. An analytical sample was obtained by recrystallization from ether-acetone, m.p. 77-79°C; NMR 1.38 (s,3H,CH_3), 2.50 and 3.25 (2d,J=18 Hz,1H each,$NCOCH_2$), 3.75 (s,2H,NCH_2CO), 4.38 (s,2H,NCH_2Ar), 5.05 (s,2H,$COCH_2Ar$), 7.35 (s,10H,ArH); IR (KBr), 1725 (ester, ketone), 1645 (amide). (Found: C, 71.49; H, 5.97; N, 4.28). Calcd. for $C_{21}H_{21}NO_4$: C, 71.79; H, 5.98; N, 3.99).

1-Benzyl-4-methyl-2,5-piperidinedione (11). A solution of 10 (1 g, 2.8 mmol) in ethyl acetate (60 ml) was hydrogenated at room temperature and atmospheric pressure over 400 mg of 10% palladium on charcoal. When the absorption ceased, the catalyst was filtered off, and the filtrate was evaporated to give 400 mg (64%) of 11. A sample recrystallized from ether melted at 92-94°C; NMR 1.10 (d,3H,CH_3), 2.2-3.0 (m,3H,3-CH_2 and C_4-H), 3.70 (s,2H,NCH_2CO), 4.50 (s,2H,NCH_2Ar), 7.10 (s,5H,ArH); IR ($CHCl_3$), 1730 (ketone), 1650 (amide). (Found: C, 71.80; H, 6.93; N, 6.57. Calcd. for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45).

Ethyl 1-Benzyl-4-benzyloxycarbonyl-2,5-dioxo-4-piperidineacetate (12). To a stirred solution of β-keto ester 5 (4 g, 11.8 mmol) in THF (85 ml) was added anhydrous potassium carbonate (3.46 g, 25 mmol) and ethyl bromoacetate (4 ml, 36 mmol) at room temperature under nitrogen. The mixture was stirred for 3-4 days as required for the reaction to be complete (negative ferric trichloride test). The mixture was diluted with water and extracted with ether. The extracts were washed successively with water, saturated sodium bicarbonate solution, and water. After evaporative bulb-to-bulb distillation to remove excess alkylating agent, the oily residue was chromatographed. Elution with 99:1 $CHCl_3/CH_3OH$ furnished 4 g (80%) of 12, b.p. 240°C/0.3 mm[27]; NMR 1.18 (t,3H,$CO_2CH_2CH_3$), 2.65 and 3.06 (2d,J=17 Hz,1H each, $NCOCH_2$), 3.06 (s,2H,CH_2CO_2Et), 3.80 (s,2H,NCH_2CO), 4.01 (q,2H,$CO_2CH_2CH_3$), 4.19 and 4.54 (2d,J= 13 Hz,1H each,NCH_2Ar), 5.02 (s,2H,CO_2CH_2Ar), 7.12 and 7.17 (2s,5H each, ArH); IR ($CHCl_3$), 1730 (ketone, ester), 1675 (amide). (Found: C, 67.90; H, 6.01; N, 3.33. Calcd. for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31).

Ethyl 1-Benzyl-2,5-dioxo-4-piperidineacetate (13). To a solution of 12 (2.3 g, 5 mmol) in ethyl acetate (170 ml) was added 10% palladium on charcoal (1.1 g), and the resulting mixture was hydrogenated at room temperature and atmospheric pressure until the solution had absorbed the required volume of hydrogen. The catalyst was removed and the solution was refluxed for 2 h. Evaporation of the solvent left 1.4 g (94%) of amido ester 13, b.p. 240°C/0.5 mm[27]; NMR 1.23 (t,3H,$CO_2CH_2CH_3$), 2.5-3.5 (m,3H,3-CH_2 and C_4-H), 2.78 (br s,2H,CH_2CO_2Et), 3.75 (s,2H,NCH_2CO), 4.08 (q,2H, $CO_2CH_2CH_3$), 4.53 (s,2H,NCH_2Ar), 7.15 (s,5H,ArH); IR (NaCl), 1730 (ester, ketone), 1660 (amide). (Found: C, 66.56; H, 6.81; N, 4.98. Calcd. for $C_{16}H_{19}NO_4$: C, 66.43; H, 6.57; N, 4.84).

Tribenzyl 1-Benzyl-4-benzyloxycarbonyl-3,6-dioxo-2,2,4-piperidinetripropionate (14). A stirred mixture of 5 (2.5 g, 7.4 mmol), benzyl 3-bromopropionate (3.8 g, 14.8 mmol) and anhydrous potassium carbonate (4.1 g, 29.6 mmol) in acetone (60 ml) was refluxed for 20 h. Additional benzyl 3-bromopropionate (3.8 g) was added, and the mixture was further refluxed for 20 h. After usual work-up and column chromatography ($CHCl_3$ as eluent), 14 was isolated as an oil (4.1 g, 50%); ^{1}H-NMR (200 MHz) 1.6-2.4 (m,12H,CH_2), 2.56 and 3.35 (2d,J=17 Hz,1H each,$NCOCH_2$), 4.27 and 4.99 (2d, J=15 Hz,1H each,NCH_2Ar), 4.90 and 4.98 (2d,J=12 Hz,1H each,$COCH_2Ar$), 4.87 and 5.09 (2d,J=12 Hz,1H each,$COCH_2Ar$), 5.03 and 5.07 (2s,2H each,$COCH_2Ar$), 7.15-7.40 (m,25H, ArH); ^{13}C-NMR: 28.6, 28.6, 28.8, 29.1, 32.6, 33.4 (t,CH_2 side chain); 36.3 (t,C-5); 45.4 (t,NCH_2Ar); 56.7 (s,C-4); 66.4, 66.6, 66.9, 68.2 (t,CO_2CH_2Ar); 72.3 (s,C-2); 167.9, 169.5, 171.6, 171.6, 171.8, 201.7 (s,CO); IR ($CHCl_3$), 1730 (ketone, ester), 1665 (amide). (Found: C, 72.59; H, 5.89; N, 2.05. Calcd. for $C_{50}H_{49}NO_{10}$: C, 72.88; H, 5.99; N, 1.70).

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