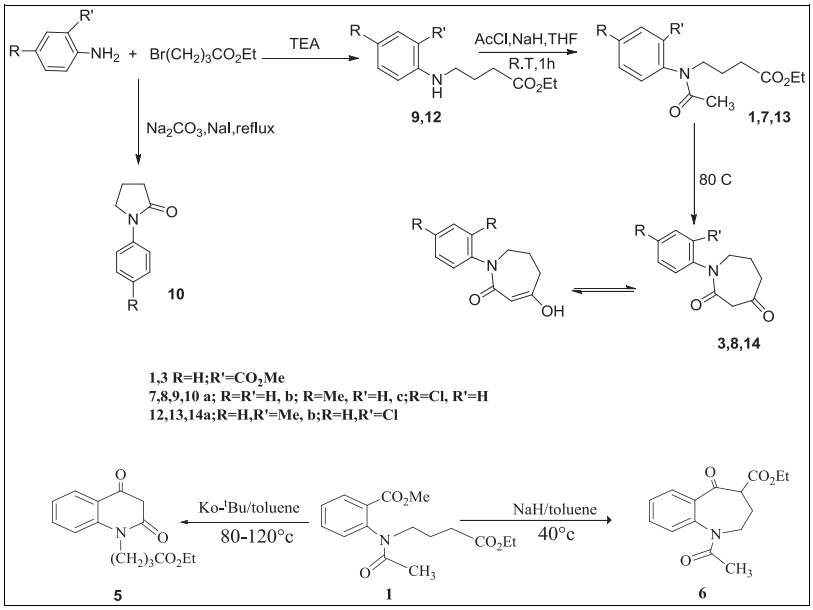
Efficient Synthesis of *N*-Substituted 2,4-Azepandione Ring System as an Active Intermediate for Heterocyclic Syntheses

Mohamed A. Waly,[a] Shiam A. Yossif,[a] Ismail T. Ibrahim,[b] and Mamdouh A. Sofan[a]*

[a]Chemistry Department, Faculty of Science, Damietta University, New Damietta 34517, Egypt
[b]Hot Laboratories Center, Atomic Energy Authority, Cairo, Egypt
*E-mail: masofan1953@du.edu.eg

Received March 22, 2016
DOI 10.1002/jhet.2709
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



An improved efficient synthesis for 2,4-azepandiones (**3**, **8**, **and 14**) could be achieved by a careful control of the reaction conditions to cyclize ethyl 4-(*N*-acetylarylamino) butanoate (**1**, **7**, **and 13**), respectively. The ethyl 4-arylamino butanoate (**9** or **12**) was prepared by stirring the ethyl 4-bromobutanoate and substituted anilines at room temperature. Then, they were acetylated with acetyl chloride and triethylamine under the conditions that avoid the formation of 2-pyrrolidinone derivatives **10**. Due to the rapid decomposition of the acetylated product (**7** or **13**) to its starting material (**9** or **12**), the reaction mixture is directly transferred without workup to the next cyclization step. The azepandione synthesis is favored by using a weak base at low temperature, where it is in a competition with the other modes of ring closure. The structures of the new compounds were supported by correct analytical and spectral data.

J. Heterocyclic Chem., **00,** 00 (2016).

INTRODUCTION

The seven-membered lactam systems were shown to be active on the central nervous system. The anticonvulsant active 4-substituted and 6-substituted caprolactams have more optimal log (partition coefficient) characteristics than the parent caprolactam itself [1,2]. Some allyl ether derivatives, which induced considerable muscular depression or paralysis, have been synthesized [3]. Also, thioketene derivatives have been used as therapeutic or prophylactic agent for hepatic diseases [4].

2,4-Azepindione ring was found in the skeleton of the anti cancer heterocyclic alkaloids, ceratamines A and B (Fig. 1), and their analogues, which were recently identified in a screen for compounds that arrest cells in mitosis [5,6]. Also, it represents the consecutive building of the bicyclic oxazolo[4,5-*c*]azepine or thiazolo[4,5-*c*]azepine ring systems [7], which act as a selective inhibitor of phosphoinositide 3-kinase [8]. Drazepinone is a potential natural herbicide [9] and the new diacetylenic natural products; montiporyne A–F compounds exhibit bioactivity against certain solid tumor cells [10]. In addition, the pyrroloazepine ring systems containing pyridinone derivative were reported as mitogen-activated protein kinase-inhibiting compounds [11].

A number of novel fused thienoazepine derivatives have been prepared and identified as potent inhibitors of MEK [12]. Moreover, the nucleosides containing a 5:7 fused ring system as a nucleobase, also known as ring- expanded nucleosides (RENs), are very interesting molecular mimics of purine nucleosides, and most of them possess significant biological activities because of their interference with the enzymes involved in the purine metabolism [13].

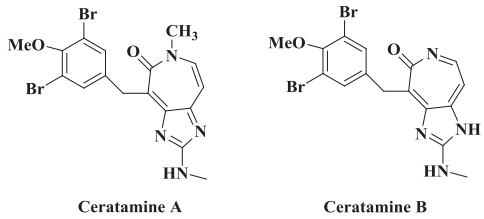


Figure 1. Ceratamine alkaloids as anticancer drug.

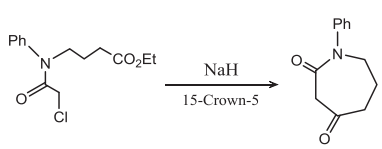
Based on the aforementioned biological significance, the 2,4-azepandione moiety became the focus of our attention. We have recently published a review article including the synthesis and biological activity for 2,4-azepandione ring system [14]. The 2,4-azepandione ring was synthesized by several procedures including one-nitrogen ring expansion such as Beckmann rearrangement for α,β-unsaturated cyclohexanone oxime derivatives with acids [15–18], thermal Curtius rearrangement, and acidic Schmidt rearrangement for the azidocyclohexanone derivatives [19,20]. The photochemical irradiation (one-carbon ring expansion) of a solution of 2,4-dioxopyridine derivative through a Pyrex filter with high-pressure mercury lamp yielded 2,4-azepenedione derivatives [21]. Also, we have published a new synthetic method for the 2,4-azepandione ring by intramolecular condensation of the *N*-acetyl-*N*-phenylaminobutanoate moiety with sodium hydride and 15-Crown-5 as a phase transfer catalyst (Scheme 1) [22].

In the present work, 2,4-azepandione was synthesized by intramolecular cyclization of ethyl N-acetyl-N-arylaminobutanoate, also the effect of the aromatic ring substituents has been studied.

RESULTS AND DISCUSSION

The earlier reported cyclization reactions of methyl *N*-acetylanthranilate were carried out with a wide variety of bases and solvents at a suitable temperature (120°C) to give 2,4-quinolindiones [23,24]. These cyclization reactions need nonaqueous solvents and a fully substituted nitrogen atom in anthranilic acid ester to avoid the intramolecular hydrogen bonding between amidic-NH and carbonyl-oxygen atom of the ester group [25]. The anions that generated from the *N*-acetyl compounds can act as electron donors for Dieckmann-like condensation reactions. The cyclization reaction of *N*-acetylanthranilic acid ester to form six-membered ring was subjected to further investigation to run a competitive study between different ring sizes and utilization of the reaction conditions to obtain a seven-membered ring.

Scheme 1



Therefore, we carried out the cyclization of the ethyl *N*-acetyl-*N*-(*o*-carbomethoxy phenyl)aminobutanoate **1** using sodium methoxide in toluene containing methanol and obtained a white crystalline product (mp 158°C) in 61% yield. This product is different than the previously reported one by Proctor *et al*. (mp 192°C) [23a]. The ^{1}H-NMR spectrum of this material revealed a singlet signal at δ 3.75 ppm corresponding to methyl ester protons and two exchangeable proton signals at δ 6.10 and 12.8 ppm that appeared as a broad band. These signals were attributed to vinylic and hydroxyl protons, respectively. This implies that the two protons on C-3 underwent enolization via the tautomeric form **4**. Also, the microanalysis showed that this compound has molecular formula $C_{14}H_{15}NO_4$. Hence, the product of our cyclization reaction of **1** is the 2,4-azepandione derivative **3**. On the other hand, structure **3** was supported as the reaction product by running competitive experiments to cyclize precursor **1** at different conditions. These experiments lead us to verify the centers that have the great potentialities for nucleophilic attack and understand the nature and versatility of this incidental cyclization of 4-(*N*-acetylarylamino) butanoate ester to the 2,4-azepandione derivatives.

Moreover, the determination of all cyclization products as a result of systematic changes in the reaction conditions (the base, solvent, and temperature) accurately will need a particular emphasis. The effect of changing of the base, solvent, and temperature was summarized in Table 1.

In the light of the previous data, a possible mechanism was suggested in Scheme 2, which illustrates the most favored mode of ring closure because of the deprotonation of the acetyl group to the carbanion **2** that attacks the ethyl ester in 7-Exo-Trig fashion [26].

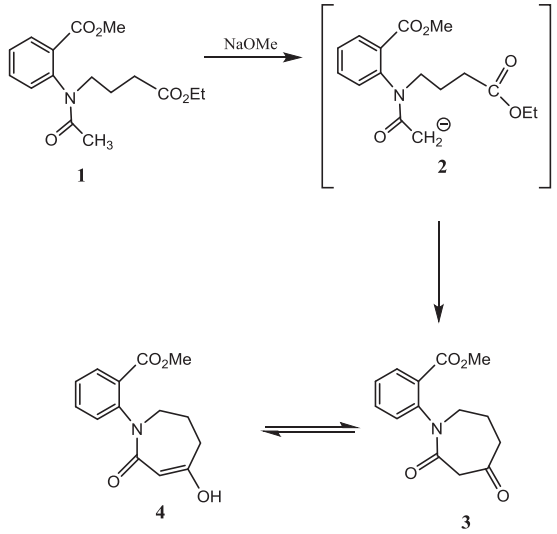
Furthermore, there are three predictable routes for ring closure of compound **1**. These are the condensation of *N*-acetyl carbanion either with butanoate ester to form 2,4-

Table 1

Effect of changing base, solvent, and temperature on the cyclization yield.

			Product %		
Base	Solvent	Temp. (°C)	**3**	**5**	**6**
$NaOCH_3$	Methanol	80	80.2	—	—
$NaOCH_3$	Toluene/ methanol	80–120	61	—	—
$NaOCH_3$	Toluene	80–120	64.8	8.7	17.4
NaH	Toluene	40	—	8.8	79
NaH	Toluene	80	—	83.6	—
t-BuOK	Toluene	25	40	—	41
t-BuOK	Toluene	80–120	—	87.2	—

Scheme 2



azepandione derivative **3** (route a) or with the aromatic ester to give 2,4-quinolindione derivative **5** (route b) and the Dieckmann condensation to produce 1-benzazepine derivative **6** (route c) (Scheme 3).

Dieckmann condensations are reversible, and the ring opening of the β-keto ester is accelerated by the presence of some alcohol in the reaction medium. The *N*-acetyl condensation (*Dieckmann*-like condensation) in the present investigation is irreversible, and the product is stable under the reaction conditions. The 2,4-azepandione (**3**, route a) was preferred where the reaction was performed in the presence of sodium methoxide as a base and methanol as a solvent. The Dieckmann condensation was retarded under these reaction conditions. When the reaction mixture was free from alcohol, the yield varied according to the kind of base and temperature used (Table 1).

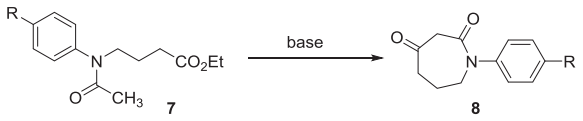
2,4-Quinolindione derivative **5** was the thermodynamically controlled product, and the yield was increased when a stronger base and elevated temperature were applied during the cyclization process and its structure had been determined and established [23a].

1-Benzazepine derivative **6** was produced under kinetically controlled conditions (equilibrium) at low temperature (40°C). The reaction equilibrium shifted to the forward direction in the absence of alcohol and at low temperature. The structure of this compound was established previously by the formation of the anion at room temperature followed by refluxing for 24 h [27].

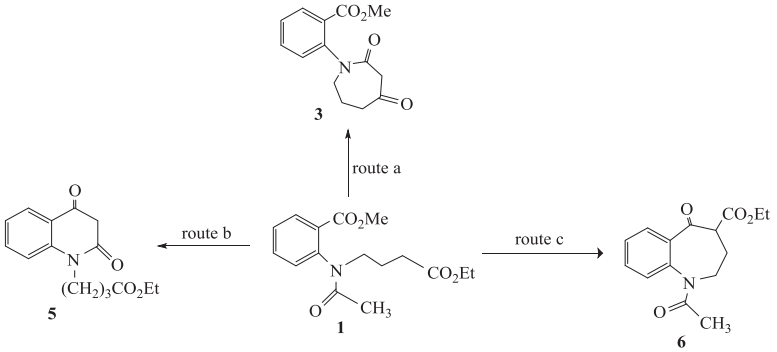
For insuring this apparent cyclization (*N*-acetyl and butanoate group to form the 2,4-azepandione ring system) without competitive feature and studying the effect of substituents on aromatic nitrogen, structure **7** with different *p*-aromatic substituents was synthesized and subjected to cyclization forming the corresponding 2,4-azepandione derivative **8** (Scheme 4).

Initially, concerning the conditions of the synthesis of compound **7** and its cyclization to 2,4-azepandione derivative **8**, heating of ethyl 4-bromobutanoate with aniline, *p*-toluidine, and/or *p*-chloroaniline under the same conditions that described for the synthesis of **1** [28] failed to give ethyl 4-(*N*-arylamino) butanoate **9a–c** as a target product and yielded the *N*-aryl-2-pyrrolidinone **10a–c** (Scheme 5). Also, stirring of the ethyl 4-bromobutanoate with anilines in tetrahydrofuran at room temperature in the presence of anhydrous sodium carbonate or triethyl amine afforded the opened structures **9**, but the reactions did not complete and the undesired 2-pyrrolidinones **10** appeared again at a long time (3 days). In continuation of our trials, sodium iodide was added to the mixture at the beginning of the reaction, which transferred to a dark place. The 4-arylaminobutanoate esters **9** were obtained in quite good yields after a relatively shorter time (24 h). We thought that sodium iodide accelerates the nucleophilic substitution reaction with 4-bromobutanoate. Finally, stirring of the reactants at room temperature without solvent in the presence of an equivalent amount of

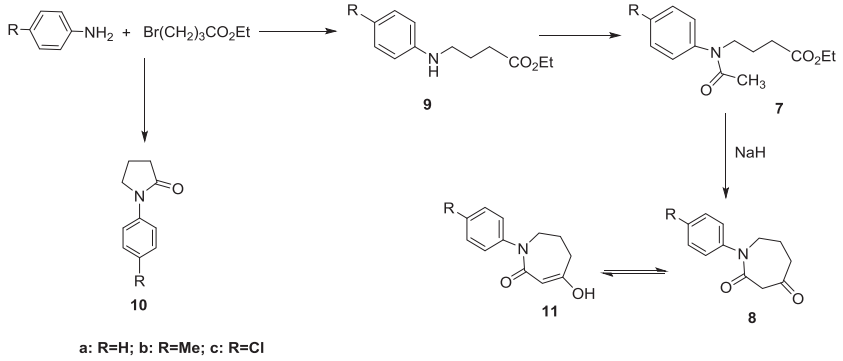
Scheme 4



Scheme 3



Scheme 5



triethylamine produced the *N*-arylaminobutanoate ester derivatives **9**. The workup for the reaction mixture should be completed with careful treatment during the extraction step of the products and evaporation of the solvent at room temperature under reduced pressure to avoid the cyclization reaction again.

The ^{1}H-NMR data showed the presence of NH proton as a broad singlet signal at δ 3.55 ppm for compounds **9a** and **9b** and at δ 3.62 ppm in the case of compound **9c**, and all of them were exchanged on treatment with D_2O. The ^{1}H-NMR spectrum for compound **10** revealed the disappearance of the ester and NH protons and the presence of three methylene protons as were pointed in experimental section for each substituent.

Attempting acetylation of compound **9** by refluxing with acetic anhydride failed to give the acetylated compound **7** and produced again the cyclized compound **10**, while stirring with acetyl chloride in THF under nitrogen afforded a new product (TLC). Unfortunately, this product was decomposed during rapid workup by addition to cold water or left in the normal atmosphere and returned back to the starting material **9**. But, this problem could be avoided by transferring the reaction mixture directly to the next cyclization step without workup.

In spite of the cyclization of precursor **7** with sodium methoxide in toluene, sodium hydride in toluene or DMF was failed; it could be cyclized to give the desired 2,4-azepandione derivative **8** in the presence of the 15-Crown-5 ether (Scheme 5). The 15-Crown-5 leads to the separation of the ions and simplifies the carbanion intramolecular nucleophilic addition to the ester group. Cyclization in THF as a solvent did not require Crown ether because it has a dual effect as a solvent and does the same role of the Crown ether. So, it was a suitable solvent for the syntheses of the target compound **8**.

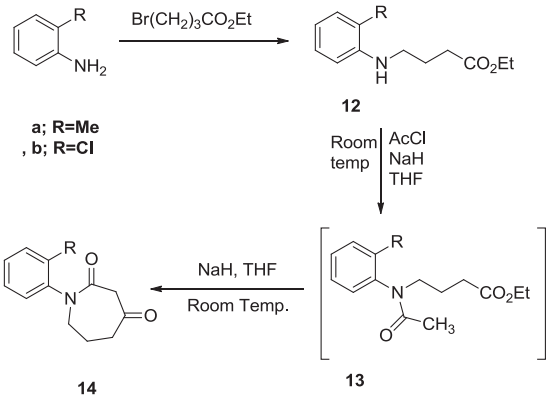
The 2,4-azepandiones **8** preferred to exist in the keto form, because their IR spectra showed the absorption bands of the amidic and carbonyl groups. The ^{1}H-NMR spectrum supported this structure by showing two protons as a singlet signals for characterizing C-3 protons without indication to the vinylic and OH protons in its enolic structure **11**. The intensity of this peak was reduced on prolonged treatment with D_2O.

For the *ortho* aniline substituents such as structure **12**, the ethyl 4-(*o*-chlorophenylamino)butanoate **12b** was prepared in a similar procedure to its *para* substituted analogue **9c** (i.e., the reaction completed at room temperature), while the 4-(*o*-methylphenylamino)butanoate derivative **12a** needed to heat the reactants in THF at 80°C and this is due to the steric hindrance exhibited by o-methyl group. The IR data for the aminobutanoate ester **12** showed the presence of both NH and C=O groups stretching, while the ^{1}H-NMR spectral data supported the presence of exchangeable NH proton at δ 3.603 and 3.998 ppm for **12a** and **12b**, respectively.

Unfortunately, the *ortho* substituted phenylaminobutanoate proceeds in the same behavior as the *para* substituted derivatives during the acetylation step to compound **13**. They were hydrolyzed in water and decomposed on heating. So, they were acetylated within the cyclization step with sodium hydride in THF to the corresponding 2,4-azepandione **14** (Scheme 6).

Also, compound **14** exists in the 1,3-diketone structure, and the C-3 protons appeared as a singlet at δ 2.958 and

Scheme 6



3.340 ppm for **14a** and **14b**, respectively. But they were completely exchanged on prolonged treatment with D_2O.

CONCLUSIONS

The synthesis of ethyl 4-[*N*-acetyl-(*p*-substituted phenyl) amino] butanoate could be achieved without its cyclization to 2-pyrrolidinone derivative by careful controlling of the reaction conditions, while the ethyl 4-[*N*-acetyl-(*o*-substituted phenyl) amino] butanoate was prepared *in situ* during the cyclization step. It was unstable in aqueous conditions or under heating and decomposed to the starting materials. Tetrahydrofuran is the suitable solvent for the intramolecular cyclization with sodium hydride without using a phase transfer catalyst (15-Crown-5), while toluene or *N*,*N*-dimethyl formamide solvent needs the presence of this catalyst.

Especially in the presence of a weak base and at low temperature, the intramolecular cyclization of the ethyl 4-(*N*-acetylarylamino)butanoate to 2,4-azepandione derivatives via 7-Exo-Trig mode of ring closure is favored than the 6-Exo-Trig that gives six-membered ring products.

EXPERIMENTAL

Melting points were obtained on digital Gallen Kamp melting point apparatus. The IR spectra were recorded on a Jasco 4100 FTIR spectrophotometer in KBr disks (υ max in cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra ($CDCl_3$) were obtained using Pucker 300-MHZ spectrometer, and chemical shift values were expressed in δ values (ppm) relative to that of the solvent. All NH and OH protons were exchangeable with D_2O. Elemental analyses were recorded on a PERKIN-ELMER 2400 C, H, N elemental analyzer, Cairo University, and mass spectra were recorded on Shimadzu QP-2010 Plus. Reaction progress was monitored by analytical TLC on precoated glass plate (silica gel 60 F_{254}-plate-Merck), and the products were visualized by UV light.

Ethyl 4-[N-acetyl-(o-carbomethoxyphenyl)amino]butanoate (**1**) was prepared according to the procedure previously described by Proctor *et al*. [27].

Cyclization procedure for ethyl 4-[*N*-acetyl-(*o*-carbome thoxyphenyl) amino] butanoate (1); synthesis of compounds 3, 5, and 6.

A. Cyclization with sodium methoxide:
   i. *In methanol/toluene*: the title compound (**1**) (3 g, 0.01 mol) in dry toluene (20 mL) and dry methanol (20 mL) was added dropwise with stirring during 15 min to sodium methoxide (from 0.23 g Na in 20-mL methanol) in dry toluene (20 mL) at 80°C. The reaction mixture was heated under reflux for 5 h at 120°C. After cooling, the solid material was extracted with cold water (30 mL × 3). The aqueous layer was separated and acidified with dil. HCl to afford the product azepandione derivative (**3**) (1.7 g, 61%).
   ii. *In methanol*: compound (**1**) (3 g, 0.01 mol) in dry methanol (20 mL) was added dropwise with stirring during 15 min to sodium methoxide (from 0.23 g Na in 20-mL methanol) at room temperature. The reaction mixture was heated under reflux for 5 h. It was concentrated under reduced pressure to nearly 10-mL methanol and left to cool, and cold water (30 mL) was added. After acidifying with diluted HCl, the solid precipitate was filtrated off, dried, and recrystallized from toluene to afford the product azepandione derivative (**3**) in 80.2% yield.
   iii. *In toluene*: precursor (**1**) (3 g, 0.01 mol) in dry toluene (30 mL) was added dropwise with stirring during 15 min to sodium methoxide (from 0.23 g of Na in 0.23-mL methanol) in dry toluene (20 mL) at 80°C. The reaction mixture was heated under reflux for 5 h at 120°C. After cooling, the solid material was extracted with cold water (30 × 3 mL). The aqueous layer was separated and acidified with dil. HCl to afford a solid product, which was filtrated and washed with cold 95% ethanol (15 mL). According to TLC investigation, the precipitate consists of two compounds that could be separated by chromatography on silica gel using (ethanol 3% + chloroform) mixture and identified as the azepandione (**3**) (1.68 g, 64.8% yield) and the 2,4-quinolinedione derivative (**5**) (0.24 g, 8.7%). The aqueous filtrate was extracted with chloroform (30 mL × 3) and dried over sodium sulfate. The chloroform was distilled, and the residue was dried under reduced pressure. The elemental and spectral data indicated that this residue is the benzazepine (**6**) (0.48 g, 17.4%).

B. Cyclization with sodium hydride:
   i. *At 40°C*: the *N*-acetylaminobutanoate **1** (3 g, 0.01 mol) in dry toluene (30 mL) was added dropwise to sodium hydride (0.89 g, 0.02 mol, 60%) in dry toluene (30 mL) at 40°C during 15 min with stirring under nitrogen. The reaction mixture was stirred under reflux at room temperature for overnight. Ethanol (5 mL) and cold water (30 mL) were added. The solid material was extracted with cold water (30 × 3 mL). The aqueous layer was separated and acidified with dil. HCl to afford a solid product, which was filtrated and washed with cold 95% ethanol (15 mL). According to TLC investigation, the precipitate consists of one compound, which could be identified as the 2,4-quinolinedione derivative (**5**) (0.62 g in 8.8% yield). The aqueous filtrate was extracted with chloroform (30 mL × 3) and dried over sodium sulfate. The chloroform was distilled, and the residue was dried under reduced pressure to give the benzazepine derivative (**6**) (2.54 g, 79%).

ii. *At 80°C*: a solution of **1** (3 g, 0.01 mol) in dry toluene (30 mL) was added dropwise during 15 min to sodium hydride (0.8 g, 0.02 mol, 60%) in dry toluene (30 mL) with stirring at 80°C under nitrogen. The reaction mixture was stirred under reflux at this temperature for further 5 h. After cooling and addition of ethanol (10 mL) and water (50 mL), the aqueous layer was separated and acidified with dil. HCl to give a white product **5** (2.3 g, 83.6%).

C. Cyclization with potassium *tert.* butoxide:

i. *Room temperature*: the amino-ester **1** (3 g, 0.01 mol) in dry toluene (30 mL) was added to a suspension of potassium *tert*. butoxide (from potassium 0.4 g in 0.74-mL *tert.* butyl alcohol) in dry toluene (30 mL) at room temperature under nitrogen during 15 min. The reaction mixture was stirred at this temperature for further 48 h. After heating under reflux for 3 min, the mixture was left to cool, and ethanol (5 mL) followed by water (50 mL) was added. The aqueous layer was separated and acidified with dil. HCl to give a precipitate, which was filtrated and identified as compound **3** (1.0 g, 40%). The aqueous filtrate was extracted with chloroform (30 mL × 3), washed with $NaHCO_3$, and dried over sodium sulfate. The chloroform was distilled, and the residue was dried under reduced pressure to give the benzazepine derivative (**6**) (1.1 g, 41%).

ii. *Refluxing temperature*: compound **1** (1.5 g, 0.05 mol) in dry toluene (20 mL) was added to a suspension of potassium *tert*. butoxide (from potassium 0.2 g in 0.37-mL *tert.* butyl alcohol) in dry toluene (20 mL) dropwise with stirring during 15 min under nitrogen. The reaction mixture was heated under reflux for 3 h at 120°C. It was left to cool, and then ethanol (10 mL) followed by water (50 mL) was added. The aqueous layer was separated and acidified with dil. HCl to give compound **5** (1.2 g, 87.2%).

1-(2-Carbomethoxyphenyl)-2,4-azepandione (3). White crystals (toluene), mp 158°C. IR: 3600 (br., OH, enolic), 1725 (CO, ester), 1640 (CO, amide) cm^{-1}; ^{1}H-NMR: δ 1.91 (m, 2H, C-6), 2.40 (t, 2H, C-5), 3.75 (s, 3H, CO_2Me), 3.85 (t, 2H, C-7), 6.10 (s, 1H, vinyl, exch.), 7.11, 7.50, 8.01 (m, t and d, 4H, ArH) and 13.10 (br., 1H, OH, enolic, exch.). *Anal.* Calcd for $C_{14}H_{15}NO_4$ (261.27): C, 64.36; H, 5.79; N, 5.36. Found: C, 63.95; H, 5.49; N, 6.10.

Ethyl 4-(2,4-dioxo-3,4-dihydroquinolin-1(2H)-yl)butanoate (5). White needles (toluene and ethanol), mp 192°C (Lit. [21a] 190–192°C); IR: 3400 (br., OH enolic), 1720 (CO, ester), 1630 (CO, amide) cm^{-1}; ^{1}H-NMR: δ 1.20 (t, 3H, $CO_2CH_2\mathbf{CH_3}$), 1.83 (m, 2H, $CH_2\mathbf{CH_2}CH_2CO_2Et$), 2.31 (t, 2H, $CH_2CH_2\mathbf{CH_2}CO_2Et$), 3.80 (t, 2H, N-$\mathbf{CH_2}CH_2-$), 4.12 (q, 2H, $CO_2\mathbf{CH_2}CH_3$), 6.16 (s, 1H, vinylic, exch.), 7.17 (m, 4H, ArH), and 11.03 (br, 1H, OH enolic) ppm. *Anal.* Calcd for $C_{15}H_{17}NO_4$ (275.30): C, 65.44; H, 6.22; N, 5.09. Found C, 65.30; H, 6.33; N, 5.23.

Ethyl 1-acetyl-5-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepine-4-carboxylate (6). bp 140°C at 0.2 mmHg [27]; IR: 1730 (CO, ester), 1690 (CO, ketone), 1630 (CO, amide) cm^{-1}; ^{1}H-NMR: δ 1.11 (q, 3H, $CO_2CH_2\mathbf{CH_3}$), 1.70 (s, 3H, $CO\mathbf{CH_3}$), 2.02 (m, 2H, CH_2-3), 3.30, 4.55 (2 m, 2H, CH_2-2), 3.71 (d, 1H, CH-4), 4.48 (q, 2H, $CO_2\mathbf{CH_2}CH_3$), 7.11 (m, 4H, ArH), and 12.60 (br., 1H, OH enolic, exch.) ppm. *Anal.* Calcd for $C_{15}H_{17}NO_4$ (275.30): C, 65.44; H, 6.22; N, 5.09. Found C, 65.25; H, 5.90; N, 4.80.

The reaction between ethyl 4-bromo butanoate and aniline derivatives (synthesis of 1-aryl-2-pyrrolidinone 10a–c). To a suspension of Na_2CO_3 (1.5 eq.) and aniline and/or its derivative (1 eq.) in MeCN (30 mL) was added ethyl 4-bromobutanoate (0.01 mol) and NaI (0.01 mol). The reaction mixture was stirred for 15 h at 20°C and then heated under reflux until completion (TLC investigation). The solvent was evaporated under reduced pressure to dryness, and the residue was partitioned between water (30 mL) and ethyl acetate (30 mL × 3). The organic layer was separated, washed with water (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The reaction product **10** was purified by chromatography on silica gel (elution with DCM/MeOH: 99/1 to 90/10).

1-Phenylpyrrolidin-2-one (10a). Yield 85.7%, mp 67–69°C; IR: 1671.22 (CO, amide) cm^{-1}; ^{1}H-NMR: δ 2.08 (m, 2H, CH_2-4), 2.51 (t, 2H, CH_2-3), 3.78 (t, 2H, CH-5), and 7.29 (m, 5H, ArH) ppm; ^{13}C-NMR: δ 18.04 (C-4), 32.76 (C-3), 48.80 (C-5), 119.99, 124.51, 128.64, 129.26, 139.42 (Ar C), 174.24 (C-2) ppm; ms: *m/z* 161.05 (21.05%), 106.05 (100%), 91.05 (21.93%), 77.00 (91.22), 65.00 (12.39%), 51 (5.83%). *Anal*. Calcd for $C_{10}H_{11}NO$ (161.20): C, 74.51; H, 6.88; N, 8.69%; found: C, 74.26; H, 6.59; N, 8.81.

1-(p-Tolyl)pyrrolidin-2-one (10b). Brownish crystals, yield 90%, mp 82°C; IR: 1687.41 (CO, amide) cm^{-1}; ^{1}H-NMR: δ 2.09 (m, 2H, CH_2-4), 2.31 (s, 3H, CH_3), 2.54 (t, 2H, CH_2-3), 3.78 (t, 2H, CH_2-5), and 7.14–7.464 (2 m, 4H, ArH) ppm; ^{13}C-NMR: δ 14.24 (CH_3), 17.97 (C-4), 32.66 (C-3), 48.90 (C-5), 113.15, 120.05, 129.31, 134.11, 136.92 (ArC), 174.10 (C-2) ppm; ms: *m/z* 175.15 (38.73%), 120.15 (100%) 91.05 (21.41%), 79.9 (20.71%), 65.00 (12.06%), 51 (4.42%). *Anal.* Calcd for $C_{11}H_{13}NO$ (175.23): C, 75.40; H, 7.48; N, 7.99; found: C, 75.66; H, 7.74; N, 8.01.

1-(4-Chlorophenyl)pyrrolidin-2-one (10c). White crystals, yield 75%, mp 90°C; IR: 1689.34 (CO, amide) cm^{-1}; ^{1}H-NMR: δ 2.08 (m, 2H, CH_2-4), 2.53 (t, 2H, CH_2-3), 3.76 (t, 2H, C-5), and 7.26–7.52 (2 m, 4H, ArH) ppm; ^{13}C-NMR: δ 18.03 (C-4), 32.84 (C-3), 48.84 (C-5), 121.18, 126.42, 128.96, 129.66, 138.22 (C-5), 174.46 (C-2) ppm; ms: *m/z* 195.05 (38.33%), 142.10 (29.91%), 140.10 (100%), 127.10 (25.54%), 111.05 (15.09%), 80 (12.72%). *Anal.* Calcd for $C_{10}H_{10}ClNO$ (195.65): C, 61.39; H, 5.15; Cl, 18.12; N, 7.16; found: C, 61.54; H, 5.70; Cl, 18.35; N, 7.74.

Synthesis of ethyl 4-(substituted phenylamino)butanoate (9a–c and 12a,b). A mixture of anilines (0.01 mol), ethyl 4-bromobutanoate (0.012 mol), and triethylamine (0.012 mol) was stirred at room temperature overnight, and then the mixture was dissolved in water (50 mL). The methylene chloride extract is washed with water and dried over sodium sulfate anhydrous. The solvent should be removed under reduced pressure at room temperature to give the crude product. Column chromatography purification using a mixture (methylene chloride : petroleum ether, 1:2) gave pure 4-anilinobutanoate derivatives **9a–c** and **12b**.

Ethyl 4-(phenyl amino)butanoate (9a). Yield 82.1%, mp 80°C; IR: 3374.82 (br., NH), 1727.91 (CO, ester) cm^{-1}; ^{1}H-NMR: δ 1.29 (t, 3H, $CO_2CH_2\mathbf{CH_3}$), 1.95 (m, 2H, N-$CH_2\mathbf{CH_2}CH_2CO_2Et$), 2.45 (t, 2H, N-$CH_2CH_2\mathbf{CH_2}CO_2Et$), 3.19 (t, 2H, N-$CH_2$), 3.81 (br, 1H, **NH** exch.), 4.17 (q, 2H, $CO_2\mathbf{CH_2}CH_3$), 6.64–7.20 (2 m, 5H, ArH) ppm; ^{13}C-NMR: δ 14.27 ($\mathbf{C}H_3CH_2$), 24.73 (C-3), 31.97 (C-2), 43.29 (C-4), 60.49 ($CH_3\mathbf{C}H_2$-), 112.73, 117.27, 129.28, 148.26 (ArC), 173.45 (C-1) ppm; ms: *m/z* 207.15 (17.27%), 162.10 (8.77%), 106.15 (100%), 91.05 (1.75%), 77.05 (17.29%), 65.00 (3.12), 51.00 (5.83). *Anal.* Calcd for $C_{12}H_{17}NO_2$ (207.13): C, 69.54; H, 8.27; N, 6.76; found: C, 69.23; H, 8.51; N, 6.85.

Ethyl 4-(4-methylphenylamino)butanoate (9b). Yield 88%, mp 54°C; IR: 3392.17 (br., NH), 1733.76 (CO, ester) cm^{-1}; ^{1}H-NMR: δ 1.27 (t, 3H, $CO_2CH_2\mathbf{CH_3}$), 1.91 (m, 2H, N-$CH_2\mathbf{CH_2}CH_2CO_2Et$), 2.28 (s, 3H, CH_3), 2.35 (t, 2H, N-$CH_2CH_2\mathbf{CH_2}CO_2Et$), 3.15 (t, 2H, N-$\mathbf{CH_2}$), 3.35 (br., 1H, **NH** exch.), 4.14 (q, 2H, $CO_2\mathbf{CH_2}CH_3$), 6.55–7.01 (2 m, 4H, ArH) ppm; ^{13}C-NMR: δ 14.54 ($\mathbf{C}H_3CH_2$), 22.84 (*p*-$\mathbf{C}H_3$), 25.08 (C-3), 32.23 (C-2), 43.90 (C-4), 60.64 ($CH_3\mathbf{C}H_2$), 113.20, 113.29, 126.53, 130.02, 130.12, 146.34 (ArC), 173.69 (C-1); ms: *m/z* 221.15 (33.23%). *Anal.* Calcd for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33; found: C, 70.67; H, 8.45; N, 6.12.

Ethyl 4-(4-chlorophenylamino)butanoate (9c). The product takes more reaction time (48 h), yield 88%, mp 52°C; IR: 3351.68 (br., NH), 1733.69 (CO, ester) cm^{-1}; ^{1}H-NMR: δ 1.26 (t, 3H, $CO_2CH_2\mathbf{CH_3}$), 1.91 (m, 2H, N-$CH_2\mathbf{CH_2}$ CH_2CO_2Et), 2.41 (t, 2H, N-$CH_2CH_2\mathbf{CH_2}CO_2Et$), 3.14 (t, 2H, N-$\mathbf{CH_2}$), 3.68 (br., 1H, **NH** exch.), 4.14 (q, 2H, $CO_2\mathbf{CH_2}CH_3$), 6.53–7.11 (2m, 4H, Ar) ppm; ^{13}C-NMR: δ 14.24 ($\mathbf{C}H_3CH_2$), 28.95 (C-3), 31.89 (C-2), 43.50 (C-4), 60.59 ($CH_3\mathbf{C}H_2$), 113.86, 116.30, 123.15, 129.12, 144.96, 146.65 (ArC), 173.43 (C-1) ppm; ms: *m/z* 241.10 (16.85%), 196.95 (17.99%), 142.10 (25.99%), 140.10 (82.18%), 127.00 (100%), 111.05 (6.54%), 79.95 (53.55%). *Anal*. Calcd for $C_{12}H_{16}ClNO_2$ (241.71): C, 59.63; H, 6.67; Cl, 14.67; N, 5.79; found: C, 60.00; H, 6.55; Cl, 14.22; N, 6.10.

Ethyl 4-[(2-chlorophenyl)amino]butanoate (12b). Yield 74%, mp 54°C; IR: 3388.32 (br., NH), 1727.56 (CO, ester) cm^{-1}; ^{1}H-NMR: δ 1.26 (t, 3H, $CO_2CH_2\mathbf{CH_3}$), 1.85 (m, 2H, N-$CH_2\mathbf{CH_2}CH_2CO_2Et$), 2.44 (t, 2H, N-$CH_2CH_2\mathbf{CH_2}CO_2Et$), 3.24 (t, 2H, N-$\mathbf{CH_2}$), 3.99 (br, 1H, **NH** exch.), 4.10 (q, 2H, $CO_2\mathbf{CH_2}CH_3$), 6.62–7.13 (2 m, 4H, ArH) ppm; ^{13}C-NMR: δ 14.22 ($\mathbf{C}H_3CH_2$), 29.71 (C-3), 31.31 (C-2), 43.03 (C-4), 60.55 ($CH_3\mathbf{C}H_2$), 111.16, 117.19, 119.13, 127.82, 129.40, 143.84 (ArC), 173.26 (c-1) ppm; ms: *m/z* 241.00 (26.66%), 196 (8.51%), 142 (31.36%), 140.00 (100%), 127.00 (11.95%), 111.05 (16.57%), 79.95 (27.82%). *Anal*. Calcd for $C_{12}H_{16}ClNO_2$ (241.71): C, 59.63; H, 6.67; Cl, 14.67; N, 5.79; found: C, 59.56; H, 6.33; Cl, 14.78; N, 5.42.

Ethyl 4-(2-methylphenylamino)butanoate (12a). After stirring the mixture of *o*-toluidine (1.07 g, 0.01 mol), ethyl 4-bromobutanoate (2.34 g, 0.012 mol), and triethylamine (1.2 mL, 0.012 mol) at room temperature for 4 h, TLC did not show any product. Then, it was dissolved in THF (30 mL) and heated gradually until reached to reflux. The reaction mixture was heated under refluxing for 8 h. It was left to cool, poured into cold water, and extracted with dichloromethane. The organic layer was separated, washed with dilute aqueous sodium hydrogen carbonate, dried over sodium sulfate, and evaporated *in vacuo* to give crude product. Column chromatography purification using a mixture (methylene chloride : petroleum ether 40–60°C, 1:2) gave the pure *ethyl 4-(o-tolylamino)butanoate* (**12a**). Yield 67, IR: 3419.17 (br., NH), 1725.98 (CO, ester) cm^{-1}; ^{1}H-NMR: δ 1.30 (t, 3H, $CO_2CH_2\mathbf{CH_3}$), 2.04 (m, 2H, N-$CH_2\mathbf{CH_2}CH_2CO_2Et$), 2.26 (s, 3H, CH_3), 2.50 (t, 2H, N-$CH_2CH_2\mathbf{CH_2}CO_2Et$), 3.29 (t, 2H, NCH_2), 3.60 (br., 1H, **NH** exch.), 4.16 (q, 2H, $CO_2\mathbf{CH_2}CH_3$), 6.71–7.18 and 7.294 (3m, 4H, ArH) ppm; ^{13}C-NMR: δ 14.49 (*o*-$\mathbf{C}H_3$), 22.64 ($\mathbf{C}H_3CH_2$), 24.60 (C-3), 32.14 (C-2), 43.51 (C-4), 60.54 ($CH_3\mathbf{C}H_2$), 115.29, 122.26, 124.97, 129.06, 130.39, 144.70 (ArC), 173.60 (C-1); ms: *m/z* 225 (100%), 221.05 (M^+, 5.65%), 176.05 (1.71%), 119.05 (13.85%), 91.05 (2.29%), 77.00 (2.29%), 65.00 (1.26%), 55.00 (6.03%). *Anal.* Calcd for $C_{13}H_{19}NO_2$ (221.30): C, 70.56; H, 8.65; N, 6.33; found: C, 70.33; H, 9.00; N, 6.54.

Acetylation of the ethyl 4-(*N*-arylamino)butanoate derivatives.

a. *By acetic anhydride*: stirring aminoester **9** (1 g) in acetic anhydride (5 mL) at room temperature for 4 h did not give any product. The reaction mixture was heated under reflux at 50°C for 2 h and then at 100°C for 4 h. After cooling, the reaction mixture was poured into cold water and extracted with dichloromethane. The organic layer was separated, washed with dilute aqueous sodium hydrogen carbonate, dried over sodium sulfate, and evaporated *in vacuo* to give crude product, which was identified as the cyclized compound **10**.

b. *By acetyl chloride*: a solution of compound **9** (1 g), acetyl chloride (2 mL), and triethylamine (1 mL) or sodium carbonate (1 g) in THF (30 mL) was stirred at room temperature for 4 h. A new product has been formed by TLC

investigation, which is completely different than the cyclized compound **10**. The reaction mixture was poured into cold water and extracted with methylene chloride. The organic layer was separated, washed with water, and dried over sodium sulfate anhydrous. The solvent was removed under reduced pressure at room temperature to give the crude product. Column chromatography purification using a mixture (methylene chloride : petroleum ether 40–60°C, 1:2) gave pure 4-anilinobutanoate derivative **9** as a result of the hydrolysis of the reaction product.

General procedure for preparation of *N*-substituted 2,4-azepandione(8 or **14**). To a mixture of ethyl 4-(*N*-arylamino)butanoate **9** and/or **13** (0.01 mol) in dry THF (50 mL) and sodium hydride (60%, 0.04 mol) at room temperature, a solution of acetyl chloride (0.01 mol) in THF (10 mL) was added with stirring under nitrogen during 10 min. The reaction mixture was stirred at this temperature for 1 h and then at 80°C for another 1 h. After cooling and adding of ethanol (excess), followed by ice cold water, the mixture was acidified with dil. HCl (2 M) and extracted with $CHCl_3$. The organic layer was separated, washed with dilute aqueous sodium hydrogen carbonate, and dried over anhydrous sodium sulfate. The solvent was evaporated to give the crude product, which purified chromatographically (dichloromethane : ethanol : ammonia, 300:8:1) to afford 2,4-azepanedione derivative **8** and or **14**.

1-Phenyl-2,4-azepandione (8a). White flacks (light petroleum bp 30–40°C), yield 79.4%, mp 50°C; IR: 1727.91 (C=O, ketone) and 1598.70 (C=O, amide) cm^{-1}; ^{1}H-NMR: δ 2.17 (q, 2H, CH_2-6), 2.23 (t, 2H, C-5), 2.25 (s, 2H, CH_2-3, exch on prolonged treatment with D_2O), 3.62 (t, 2H, CH_2-7) and 7.04 (m, 5H, ArH) ppm; ^{13}C-NMR: δ 23.09 (C-6), 44.29 (C-5), 48.13 (C-7), 50.08 (C-3), 119.61, 123.47, 127.82, 127.69, 128.61, 142.90 (ArC), 170.10 (C-2), 172.97 (C-4) ppm; ms: *m/z* 203.10 (0.14%), 161.10 (27.10%), 106.10 (90.28%), 91.05 (4.36%), 79.95 (100%), 63.95 (48%), 51.00 (10.08). *Anal.* Calcd for $C_{12}H_{13}NO_2$ (203.24): C, 71.92; H, 6.45; N, 6.89, found: C, 72.32; H, 6.63; N, 6.55.

1-(p-Tolyl)-2,4-azepandione (8b). White flacks (light petroleum bp 30–40°C), yield 65%, mp 68–70°C; IR: 1737.55 (C=O, ketone) and 1671.68 cm^{-1} (C=O, amide) cm^{-1}; ^{1}H-NMR: δ 2.00 (q, 2H, CH_2-6), 2.26 (t, 2H, CH_2-5), 2.32 (s, 3H, CH_3), 2.49 (s, 2H, CH_2-3, exch on prolonged treatment with D_2O), 3.69 (t, 2H, CH_2-7), 6.99–7.44 (m, 4H, ArH) ppm; ^{13}C-NMR: δ 18.10 (*p*-**C**H_3), 21.01 (C-6), 32.84 (C-5), 48.41 (C-7), 49.07 (C-3), 120.18, 129.36, 133.27, 134.27, 136.61, 137.12 (ArC), 169.09 (C-2), 174.27 (C-4); ms: *m/z* 217.00 (62.79%), 177.00 (62.79%), 153.00 (90.71%), 120.00 (75.58%), 92.00 (69.77%), 82.00 (97.67%), 66.00 (72.09%), 51.00 (100%). *Anal.* Calcd for $C_{13}H_{15}NO_2$ (217.26): C, 71.87; H, 6.96; N, 6.45, found: C, 72.01; H, 6.72; N, 6.19.

1-(4-Chlorophenyl)-2,4-azepandione (8c). White flacks (light petroleum bp 30–40°C), yield 81%, mp 61°C; IR: 1725.53 (C=O, ketone) and 1644.98 (C=O, amide) cm^{-1}; ^{1}H-NMR: δ 2.14 (q, 2H, CH_2-6), 2.59 (t, 2H, CH_2-5), 2.88 (s, 2H, CH_2-3, exch on prolonged treatment with D_2O), 3.81 (t, 2H, CH_2-7) and 7.23–7.56 (m, 4H, ArH) ppm; ^{13}C-NMR: δ 22.77 (C-6), 32.62 (C-5), 48.70 (C-7), 51.15 (C-3), 121.04, 128.85, 128.90, 129.57, 136.82, 137.94 (C-3), 169.13 (C-2), 174.37 (C-7) ppm; ms: *m/z* 237.10 (1.66%), 195.05 (22.23%), 142.05 (21.03%), 140.10 (67.44%), 127.10 (2.46%), 111.05 (11.04%), 79.95 (100%). *Anal.* Calcd for $C_{12}H_{12}ClNO_2$ (237.68): C, 60.64; H, 5.09; Cl, 14.92; N, 5.89, found: C, 60.71; H, 5.32; Cl, 15.11; N, 6.15.

1-(o-Tolyl)-2,4-azepandione (14a). Oily product, yield 68%; IR 1729.83 (C=O, ketone) and 1648.84 (C=O, amide) cm^{-1}; ^{1}H-NMR: δ 1.92 (q, 2H, CH_2-6), 2.29 (t, 2H, CH_2-5), 2.32 (s, 3H, CH_3), 2.95 (s, 2H, C-3, exch on prolonged treatment with D_2O), 3.69 (t, 2H, CH_2-7) and 7.11–7.43 (m, 4H, ArH) ppm; ^{13}C-NMR: δ 17.61 (*o*-**C**H_3), 22.44 (C-6), 31.85 (C-5), 47.47 (C-7), 52.46 (C-3), 125.90, 128.75, 129.42, 130.27, 136.16, 140.21 (ArC), 170.84 (C-2), 172.98 (C-4) ppm; ms: *m/z* 217.10 (3.61%), 177.10 (5.98%), 153.10 (8.17%), 120.10 (14.22%), 91.05 (14.64%), 77.00 (24.56%), 65.00 (11.57%), 55.05 (100%). *Anal.* Calcd for $C_{13}H_{15}NO_2$ (217.26): C, 71.87; H, 6.96; N, 6.45, found: C, 71.55; H, 7.12; N, 6.63.

1-(2-Chlorophenyl)-2,4-azepandione (14b). Oily product, yield 78%, IR: 1722.12 (C=O, ketone) and 1656.55 (C=O, amide) cm^{-1}; 1H-NMR: δ 2.17 (q, 2H, CH_2-6), 2.31 (t, 2H, CH_2-5), 3.34 (s, 2H, CH_2-3, exch on prolonged treatment with D_2O), 3.92 (t, 2H, CH_2-7), 6.97–7.22 (m, 4H, ArH) ppm; ^{13}C-NMR: δ 22.91 (C-6), 31.59 (C-5), 47.63 (C-7), 51.08 (C-3), 122.77, 128.29, 129.57, 130.16, 132.95, 139.67 (ArC), 169.27 (C-2), 173.02 (C-4); ms: *m/z* 237.10 (1.66%), 196.00 (9.92%), 142,05 (31.94%), 140.10 (100%). 127.05 (14.40%), 111.05 (10.27%), 79.95 (27.82%). *Anal.* Calcd for $C_{12}H_{12}ClNO_2$ (237.68): C, 60.64; H, 5.09; Cl, 14.92; N, 5.89, found: C, 60.33; H, 4.92; Cl, 14.55; N, 5.75.

REFERENCES AND NOTES

[1] Elison, C.; Lien, E. J.; Zinger, A. P.; Hussain, M.; Tong, G. L.; Golden, M. J Pharm Sci 1971, 60, 1058.

[2] Lien, E. J.; Lien, L. L.; Tong, G. L. J Med Chem 1971, 14, 846.

[3] Mooney, B. A.; Prager, R. H.; Ward, A. D. Aust J Chem 1980, 33, 2717.

[4] Ikuo, I.; Koichi, H.; Yutaka, S.; Yuzo, M.; Mamoru, M. Eur Pat Appl 1985, 149, 534(CI CO7D09/04).

[5] (a) Coleman, R. S.; Campbell, E. L.; Carper, D. J US Pat Appl Publ 2012, 8, 183 365B2; (b) Coleman, R. S.; Campbell, E. L.; Carper, D. J. US Pat Appl Publ 2010 20100234588A1; (c) Nodwell, M.; Pereira, A.; Riffell, J. L.; Zimmerman, C.; Palrick, B. O.; Roberge, M.; Andersen, R. J. J Org Chem 2009, 74, 995; (d)

Coleman, R. S.; Campbell, E. L.; Carper, D. J. Org Lett 2009, 11, 2133.

[6] (a) Karjala, G.; Chan, Q.; Manzo, E.; Andersen, R. J.; Roberge, M. Cancer Res 2005, 65, 3040; (b) Manzo, E.; Van Soest, R.; Matainaho, L.; Roberge, M.; Andersen, R. Org Lett 2003, 5, 4591.

[7] (a) Conn, P. J.; Lindsley, C. W.; Stauffer, S. R.; Jones, C. K.; Bartolome-Nebreda, J. M.; Conde-Ceide, S.; MacDonald, J. G.; Vaca, M. J. WO2012031024 A1, 2013; (b) Macdonald, G. J.; Trabanco-Suarez, A. A.; Conde-Ceide, S.; Tresadern, G. J.; Bartolome-Nebreda, J. M.; Pastor-Fernandez, J. WO 2011073339 A1, 2011; (c) Denonne, F.; Celanire, S.; Provins, L.; Defays, S. WO 2008012010 A1, 2008.

[8] Alexander, R.; Balasundaram, A.; Batchelor, M.; Brookings, D.; Crépy, K.; Crabbe, T.; Deltent, M. F.; Driessens, F.; Gill, A.; Harris, S.; Hutchinson, G.; Kulisa, C.; Merriman, M.; Mistry, P.; Parton, T.; Turner, J.; Whitcombe, I.; Wright, S. Bioorg & Med Chem Lett 2008, 18, 4316.

[9] Evidente, A.; Andolfi, A.; Vurro, M.; Fracchiolla, M.; Zonno, M. C.; Motta, A. Phytochemistry 2005, 66, 715.

[10] (a) Chen, J. Thesis, Rochester Institute of Technology, 2005; (b) Collison, C. G.; Chen, J.; Walvoord, R. Synthesis 2006, 14, 2319; (c) Jing-lai, H.; Wei, L.; Qiong, X.; Yan, C.; Zhui-bai, Q. Fudan Xuebao/Yixueban 2005, 32, 173; (d) Zhuibai, Q.; Wang, H.; Xia, Z.; Lu, M. PCT/EP2007/006338, 2008.

[11] Anderson, D. R.; Mahoney, M. W.; Phillion, D. P.; Rogers, T. E.; Meyers, M. J.; Poda, G.; Hegde, S. G.; Singh, M.; Reitz, D. B.; Wu, K. K.; Buchler, I. P.; Xie, J.; Vernier, W. F. WO2004058762 A1, PCT/ US 2003040811 2004 CA 2509565A1.

[12] (a) Satake, K.; Itoh, K.; Miyoshi, Y.; Kimura, M.; Morosawa, S. J Chem Soc Perkin Trans 1 1986, 729; (b) Laing, V. E.; Brookings, D. C.; Carbery, R. J.; Gascon, S. J. M.; Hutchings, M. C.; Langham, B. J.; Lowe, M. A. WO2008020206A2, PCT/ GB 2007/003114 2008 EP 2054417A2; (c) Laing, V. E.; Brookings, D. C.; Carbery, R. J.; Simorte, J. G.; Hutchings, M. C.; Langham, B. J.; Lowe, M. A.; Allen, R. A.; Fetterman, J. R.; Turner, J.; Meier, C.; Kennedy, J.; Merriman, M. Bioorg & Med Chem Lett 2012, 22, 472.

[13] D'Errico, S.; Oliviero, G.; Amato, J.; Borbone, N.; Cerullo, V.; Hemminki, A.; Piccialli, V.; Zaccaria, S.; Mayola, L.; Picciallia, G. Chem Commun 2012, 48, 9310.

[14] Waly, M. A.; Yossif, S. A.; Sofan, M. A.; Ibrahim, I. T. Synthetic Commun 2015, 45, 1823.

[15] (a) Donat, F.– J.; Nelson, A. I. J Org Chem 1957, 22, 1107; (b) Pinder, R. M. J Chem Soc 1969 1690; (c) Teuber, H. J.; Cornclius, D.; Wolcke, U. Justus Liebigs Ann 1966, 696, 116; (d) Singh, H.; Parashar, V. V.; Padmanbhan, S. J Sci Induster Res 1966, 25, 208; (e) Shroff, A. P.; Harper, C. H. J Med Chem 1969, 12, 190; (f) Ahmed, M. S.; Siddiqui, A. H.; Shafiullah; Logan, S. C. Aust J Chem 1969, 22, 271.

[16] (a) Mazur, R. H. J Org Chem 1961, 26, 1289; (b) Montgomery, R. S.; Dougherty, G. J Org Chem 1952, 17, 823; (c) Hester, J. B. Jr. J Org Chem 1970, 35, 875; (d) Hester, J. B. Jr. J Org Chem 1967, 32, 3804.

[17] Tamura, Y.; Kita, Y.; Terashima, M. Chem Pharm Bull 1971, 19, 529.

[18] Tamura, Y.; Kita, Y.; Uraoka, J. Chem Pharm Bull 1972, 20, 876.

[19] Tamura, Y.; Oshimura, Y.; Kita, Y. Chem Pharm Bull 1972, 20, 871.

[20] Tamura, Y.; Kita, Y. Chem Pharm Bull 1971, 19, 1735.

[21] (a) Sato, S.; Ikeda, Y.; Kanaoka, Y. Chem Pharm Bull 1983, 31, 1362; (b) Sato, S. Bull Chem Soc Japan 1968, 41, 2524.

[22] Waly, M. A. J. Park Chem 1994, 336, 86.

[23] (a) Cromarty, A.; Proctor, G. R.; Shabbier, M. S. J Chem Soc Perkin I 1972 2012; (b) Ashley, J. N.; Perkin, W. H.; Robinson, R. J Chem Soc 1930 382.

[24] McDonald, B. G.; Proctor, G. R J Chem Soc Perkin I 1975, 1446.

[25] Rae, J. D. Can J Chem 1968, 46, 2589.

[26] Baldwin, J. E. J Chem Soc, Chem Comun 1976, 734.

[27] Proctor, G. R.; Ross, W. I.; Tapia, A. Chem Soc Perkin I 1972, 1803.

[28] McCall, I.; Proctor, G. R.; Purdie, L. J. Chem Soc(C) 1970, 1126.