Synthesis of pyrrolo[1,2-α]indole-1,8(5H)-diones as new synthons for developing novel tricyclic compounds of pharmaceutical interest

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Dedicated to Professor Vincenzo Tortorella in the occasion of his “Fuori Ruolo” status
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Abstract
In the course of our work aimed at developing novel heterocycles of pharmaceutical interest, a new tricycle, the tetrahydropyrrolo[1,2-α]indole-1,8-dione, has been synthesized by an intramolecular Friedel-Crafts acylation, as a synthon suitable to be functionalized to give novel compounds with potential biological properties. Also, an unusual nucleophilic α-addition to methyl propiolate by 1,5,6,7-tetrahydro-4H-indol-4-one was observed and discussed.

Keywords: Tetrahydropyrrolo-[1,2-α]indole-1,8-dione, intramolecular Friedel-Crafts, Michael-type α-addition

Introduction
The production of heterocyclic compounds is dominating in the field of modern organic and medicinal chemistry. In particular the presence of heterocycles in drugs represents the majority of known pharmaceutical preparations. For these reasons our team has for a long time been interested in the synthesis of new heterocycles to be employed as new pharmaceutical agents.

In this context many types of heterocycle have been described by some of us and their chemistry adequately investigated.1-4 More recently, our attention focused on the preparation of pyrrolo[g]indoles from which the present investigation began. The observation that the bis adduct of 4,5,6,7-tetrahydroindole-4-ketoxime with methyl propiolate (MP) 1 underwent thermal retro-Michael addition of MP to give E-2 in 22% yield5 prompted us to find a new procedure for the preparation of 2 (Figure 1). This intermediate has been first considered a key synthon for a conversion into pyrrolo[1,2-α]indole-1,8(5H)-dione 3a which, by reduction of its 2,3-double
bond, could be converted into 3b (Figure 1), both potential substrates for drug design. In fact this three-ring system possesses a peculiar feature to be purposely functionalized via the two oxo groups into possible intercalating agents which are in our mind. The endeavours to obtain this skeleton are the object of this communication.

![Figure 1. Design of target compounds.](image)

**Results and Discussion**

**Chemistry**

An overall view of the attempts made and the synthetic routes employed to prepare the targets tricycles 3a,b are presented in Schemes 1-3. Attempted preparation of 2 by carrying out a Michael addition of 4 on methyl propiolate (MP) in dichloromethane and in the presence of triphenylphosphine (TPP), adapting a method previously described by other authors, failed. This failure was surprising since it is well known that the addition of electron poor nucleophiles to activated olefins is strongly dependent on the base. However, there have been several reports that this addition does occur to activated vinyl phosphorus systems. Thus, in contrast to the expected acrylate 2, we obtained regioselectively the vinyl ester 5 in 78% yield (Scheme 1). The structure of 5 was unambiguously assigned on the basis of its elemental analysis and EI-mass as well as by the data of 1H- and 13C-NMR experiments. Its 1H-NMR spectrum was recorded in various organic solvents in order to evaluate a possible variation of the chemical shifts of olefinic protons. In particular, at 200 MHz in CDCl3 it exhibited two singlets at δH = 6.54 and 5.88 while the corresponding spectra registered in DMSO-d6 and acetone-d6 revealed two doublets at δH = 6.52 and 6.12 and at δH = 6.53 and 6.04, respectively. Both splitting patterns for the methylene protons appeared weakly coupled with a constant of 3JHH = 1.2 (in DMSO-d6) and 1.0 Hz (in acetone-d6), thus indicating that neither E or Z adduct was formed. HETCOR experiments confirmed that the two protons are correlated with the same carbon located at δC = 124.8 also well evidenced by DEPT/APT spectra. This value for a methylene in the β-position of a vinyl ester was consistent with the predictions of Kalinowski et al. that locate the CH2 chemical shift...
at about 125 ppm. Besides $^{13}$C-NMR TOTAL COUPLING further confirmed the presence of the CH$_2$ showing a double doublet centered at 124.8 ppm. Moreover, NOESY and NOE difference experiments showed NOE correlations between the aromatic H-2 and H$_A$-hydrogen of the methylene in $\beta$-position. These experiments distinguished the two methylene protons (Figure 2). In fact, according to our prediction, no NOE interactions between H-2 and H$_B$ protons could be observed for compound 5.

In order to circumvent this unexpected behavior, we performed the reaction in DMSO using TEA as catalyst, that afforded stereoselectively 2 as $E$- isomer in 36% yield (Scheme 1). The chemical and spectroscopic properties of this compound were coincident with those previously reported by us.$^5$

Scheme 1. Reagents and conditions: A) MP, TPP, CH$_2$Cl$_2$, r.t. for 10 h; B) MP, TEA, DMSO, 55 °C for 24 h.

Figure 2. NOE correlations for compound 5.

In the light of this result, it was interesting to postulate a mechanism for the formation of 5. Previous studies$^{8,9}$ described an initial attack of TPP to the $\beta$-carbon of MP to give the phosphonium enolate intermediate 6 and concomitant protonation of this 1:1 adduct to form the
corresponding phosphonium salt 7. In a second step a β-addition by the nucleophile anion takes place followed by elimination of the phosphine, to be recycled as a catalyst, to afford the β-acrylates. In the our case, although the nucleophilic β-addition was potentially most favourable for the major electrophilicity of the β-carbon of the adduct 7, we observed that the conjugate addition of 4 proceeded through an unusual Michael-type α-addition to the β-triphenylphosphonium acrylate counterpart. A possible explanation of this result may be due to steric hindrance of the phosphine moiety in proximity of the β-carbon of the adduct and consequently the anion 4 would attack the more free α-carbon. This assumption could be supported from the fact that compound 2 was easily obtained following other reaction conditions.

\[
(\text{Ph})_3\text{P} + \text{HC} = \text{C} = \text{CO}_2\text{Me} \\
\downarrow \\
(\text{Ph})_3\text{P}^+\text{CH} = \text{C} = \text{C} = \text{O}^- \text{OMe} \\
\downarrow \\
(\text{Ph})_3\text{P}^+\text{CH} = \text{CH} = \text{COOMe} \\
\downarrow \\
\beta \\
\alpha \\
6 \\
7 \\
5
\]

**Figure 3.** Proposed mechanism for the formation of 5.

Although the propenoate 2 has been obtained only in \(E\)-configuration we thought that an intramolecular cyclization of the opportune more electrophilic acid derivative could easily lead to 3a. With this in mind we saponified\(^{13}\) the ester group of \(E\)-2 to obtain the acid \(E\)-8 that might undergo ring closure in the presence of polyphosphoric acid (PPA)\(^{14-16}\) or PCl\(_5\)\(^{17}\) (Scheme 2). Unfortunately, probably due to the unfavourable stereochemistry of the precursor, this reaction failed, preventing the expected hydrogenation of the olefinic double bond to obtain the analogue 3b.

\[
\text{E-2} \xrightarrow{i} \text{E-8} \xrightarrow{\text{ii}} \text{3a} \xrightarrow{\text{rid}} \text{3b}
\]

**Scheme 2.** Reagents and conditions: (i) LiOH·H\(_2\)O (4 eq.), H\(_2\)O/THF, r.t. for 1 h, then 2N HCl. (ii) a] 84% PPA, 90 °C for 12 h or b] PCl\(_5\), anhydr. CH\(_2\)Cl\(_2\), r.t. for 12 h.

This fact suggested that we must obtain 3b by another synthetic route. Then, we alkylated 4 with acrylonitrile in dioxane and in the presence of triton B\(^{18, 19}\) to afford 9 in 74% yield. The
latter on hydrolysis\textsuperscript{20} gave the acid 10 that by an intramolecular Friedel-Crafts cyclization in PPA at 90 °C gave the desired diketone 3b in 85% yield (Scheme 3), which was characterized by several NMR methods (\textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR, DEPT/APT, HETCOR).

Scheme 3. Reagents and conditions: (i) Acrylonitrile, Dioxane, 40\% Triton B, r.t. for 2 h. (ii) KOH sol., reflux for 1 h, then 2N HCl. (iii) 84\% PPA, 90 °C for 2.5 h.

At this stage we explored the reactivity of these carbonyl functions by converting 3b into the diketoxime 11 (Scheme 4) and alternatively we investigated the possibility of a selective reduction of one of the two carbonyl of 3b into CH\textsubscript{2} in order to functionalize the derived mono-ketone. Thus, we attempted a modified Wolff-Kishner reaction\textsuperscript{21} on 3b and found that it was regioselectively reduced to give the ketone 12 (Scheme 4).

Scheme 4. Reagents and conditions: (i) NH\textsubscript{2}OH·HCl, CH\textsubscript{3}COONa, EtOH/H\textsubscript{2}O 2:1, reflux for 6 h. (ii) 98\% Hydrazine hydrate, KOH pellets, Diethylene glycol, reflux for 1.5 h, next 195 °C for 4 h.

Conclusions

This work describes a versatile synthesis of a new heterocycle system bearing two carbonyl functions located in a convenient orientation to be variously derivatized. The geometry of this
tricyclic framework as well as its possible modification were by us considered very important features from a medicinal chemistry point of view. In fact, in conjunction with this chemical effort, work is in progress to prepare a library of mono- and disubstituted derivatives of 3b which will be submitted to biological testing in the anticancer field. Also, further studies are in progress in order to better investigate the particular α-addition to acetylenic esters.

**Experimental Section**

**General Procedures.** Anhydrous solvents and all reagents were purchased from Aldrich, Merck or Carlo Erba. All reactions involving air- or moisture-sensitive compounds were performed under nitrogen atmosphere using oven-dried glassware and syringes to transfer solutions. Melting points (m.p.) were determined using an Electrothermal melting point or a Köfler apparatus and are uncorrected. Infrared (IR) spectra were recorded as thin films or nujol mulls on NaCl plates with a Perkin-Elmer 781 IR spectrophotometer and are expressed in ν (cm⁻¹). Nuclear magnetic resonance (¹H-NMR, ¹³C-NMR, ¹³C-NMR TOTAL COUPLING, DEPT/APT, HETCOR, NOESY and NOE difference) spectra were determined in CDCl₃, DMSO-d₆ or CDCl₃/DMSO-d₆ (in the ratio 1:3) and Acetone-d₆ and were recorded on a Varian XL-200 (200 MHz). Chemical shifts (δ scale) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; bs, broad singlet; dd, double doublet. The assignment of exchangeable protons (OH and NH) was confirmed by the addition of D₂O. Electron ionization mass spectra (70 eV) were recorded on a Hewlett-Packard 5989 Mass Engine Spectrometer. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel F-254 plates. Pure compounds showed a single spot on TLC. For flash chromatography Merck Silica gel 60 was used with a particle size 0.040-0.063 mm (230-400 mesh ASTM). Elemental analyses were performed on a Perkin-Elmer 2400 instrument at Laboratorio di Microanalisi, Dipartimento di Chimica, Università di Sassari (Italy), and the results were within ±0.4% of the theoretical values.

**Methyl 2-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)acrylate (5).** To a magnetically stirred solution of 1,5,6,7-tetrahydro-4H-indol-4-one 4 (2 g, 14.8 mmol) and TPP (0.97 g, 3.7 mmol) in 20 mL of dichloromethane, a solution of MP (1.24 g, 1.31 mL, 14.8 mmol) in 10 mL of CH₂Cl₂ was added at 0 °C dropwise over a period of 15 min. The reaction solution was then allowed to warm up to room temperature and stirred for 10 h. Subsequently the solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica gel (eluent: Petroleum Ether/Ethyl Acetate 5:5) to obtain the compound 5 as a pale yellow solid (78%), mp 78-79 °C; Rᵋ = 0.46 (petroleum ether/ethyl acetate 5:5): IR (nujol) ν cm⁻¹ = 1730 (C=O), 1660 (C=O), 1645 (C=C).
NMR data: \( \delta_H \) (CDCl\(_3\)) 6.62 (s, 2H, Ar-H x 2), 6.54 (s, 1H, C=CH\(_B\)), 5.88 (s, 1H, C=CH\(_A\)), 3.87 (s, 3H, OCH\(_3\)), 2.64 (t, 2H, CH\(_2\)), 2.50 (t, 2H, CH\(_2\)), 2.12 (m, 2H, CH\(_2\)).

\( \delta_H \) (DMSO-\( d_6\)) 6.88 (d, 1H, Ar-H, \( J = 3.2 \) Hz), 6.52 (d, 1H, C=CH\(_B\), \( J = 1.2 \) Hz), 6.38 (d, 1H, Ar-H, \( J = 3.2 \) Hz), 6.12 (d, 1H, C=CH\(_A\), \( J = 1.2 \) Hz), 3.79 (s, 3H, OCH\(_3\)), 2.61 (t, 2H, CH\(_2\)), 2.35 (t, 2H, CH\(_2\)), 2.00 (m, 2H, CH\(_2\)).

\( \delta_H \) (Acetone-\( d_6\)) 6.79 (d, 1H, Ar-H, \( J = 3.2 \) Hz), 6.53 (d, 1H, C=CH\(_B\), \( J = 1 \) Hz), 6.42 (d, 1H, Ar-H, \( J = 3.2 \) Hz), 6.04 (d, 1H, C=CH\(_A\), \( J = 1 \) Hz), 3.83 (s, 3H, OCH\(_3\)), 2.67 (t, 2H, CH\(_2\)), 2.35 (t, 2H, CH\(_2\)), 2.06 (m, 2H, CH\(_2\)).

\( \delta_C \) (CDCl\(_3\)) 194.4 (C=O), 162.9 (\( \alpha \)-C=), 144.1 (C-7a), 135.7 (C-3a), 124.8 (\( \beta \)-CH\(_2\)), 123.5 (C-2), 106.0 (C-3), 52.9 (OCH\(_3\)), 37.6 (C-5), 22.3 (C-6).


**Methyl (2E)-3-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)acrylate (E-2).** To a stirred solution of the ketone 4 (2 g, 14.8 mmol) in dry DMSO (90 mL), containing TEA (1 mL), was added dropwise at 0-5 °C a solution of MP (2.57 g, 2.73 mL, 29.6 mmol) in dry DMSO (10 mL). The resulting solution was heated at 55 °C for 24 h. After cooling, the mixture was poured into ice and extracted several times with dichloromethane. The organic layer was washed with water and dried over anhydrous sodium sulfate. On evaporation in vacuo an oily residue was obtained and purified by flash column chromatography on silica gel (eluent: CH\(_2\)Cl\(_2\)/MeOH 9:1) to obtain the desired compound E-2 as a beige solid (36%), mp 138-140 °C (lit 5 140-142 °C); \( R_f \) = 0.88 (CH\(_2\)Cl\(_2\)/MeOH 9:1); IR (nujol) \( \nu \) cm\(^{-1}\) = 1720 (C=O), 1680 (C=O), 1615 (C=C).

NMR data: \( \delta_H \) (CDCl\(_3\)) 7.85 (d, 1H, NC\(_H\)=CH (E), \( J = 14.2 \) Hz), 6.97 (d, 1H, H-2, \( J = 3.4 \) Hz), 6.69 (d, 1H, H-3, \( J = 3.4 \) Hz), 6.00 (d, 1H, NCH=C (E), \( J = 14.2 \) Hz), 3.81 (s, 3H, OCH\(_3\)), 2.90 (t, 2H, H-5), 2.52 (t, 2H, H-7), 2.22 (qn, 2H, H-6). \( \delta_C \) (CDCl\(_3\)) 193.9 (C=O), 166.7 (C=O), 144.1 (C-7a), 136.8 (\( \alpha \)-C=), 123.3 (C-3a), 118.7 (\( \beta \)-CH\(_2\)), 109.4 (C-2), 105.3 (C-3), 51.8 (OCH\(_3\)), 37.6 (C-5), 22.3 (C-6). GC/MS = 219 \([M+H]^+\). Anal. Calcd. for C\(_{12}\)H\(_{13}\)NO\(_3\) (219.237): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.66; H, 6.18, N, 6.61.

**(2E)-3-(4-Oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)acrylic acid (E-8).** To a solution of methyl (2E)-3-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)acrylate E-2 (0.69 g, 3.15 mmol) in THF (15 mL) a solution of LiOH (0.53 g, 12.6 mmol) in water (15 mL) was added. The mixture was stirred at room temperature for 1.5 h. After removal of THF in vacuo, the basic aqueous residue was cooled at 0-5 °C and then neutralized with 2N HCl. The white precipitate formed was filtered off, washed with water and recrystallized from ethanol-water to afford the desired compound E-8 (96%) as white crystals, mp 227-229 °C; \( R_f \) = 0.39 (CH\(_2\)Cl\(_2\)/MeOH 9:1); IR (nujol) \( \nu \) cm\(^{-1}\) = 1710 (C=O), 1660 (C=O), 1605 (C=C).

NMR data: \( \delta_H \) (CDCl\(_3\) + DMSO-\( d_6\)) 7.83 (d, 1H, NCH=CH (E), \( J = 14.2 \) Hz), 7.04 (d, 1H, H-2, \( J = 3.2 \) Hz), 6.64 (d, 1H, H-3, \( J = 3.2 \) Hz), 6.02 (d, 1H, NCH=CH (E), \( J = 14.2 \) Hz), 2.90 (t, 2H, H-5), 2.50 (t, 2H, H-7), 2.21 (qn, 2H, H-6). GC/MS = 205 \([M+H]^+\). Anal. Calcd. for C\(_{11}\)H\(_{11}\)NO\(_3\) (205.210): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.49; H, 5.66, N, 6.72.
3-(4-Oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)propanenitrile (9). To a magnetically stirred solution of 1,5,6,7-tetrahydro-4H-indol-4-one 4 (2.20 g, 16.3 mmol) and Triton B (40% benzyltrimethylammonium hydroxide sol. in water) (0.22 mL, 1.4 mmol) in dioxane (15 mL), acrylonitrile (0.95 g, 1.18 mL, 18 mmol) was slowly added over a period of 45 min. The reaction mixture was stirred at room temperature for 2 h. Then, the solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica gel (eluent: Petroleum Ether/Ethyl Acetate 7:3) to obtain 9 as a pale orange solid (74%), mp 81-83 °C; Rf = 0.21 (Petroleum Ether/Ethyl Acetate 7:3); IR (nujol) ν cm⁻¹ = 2250 (CN), 1720 (C=O), 1630 (C=C). NMR data: δH (CDCl₃) 6.66 (d, 1H, Ar-H), 6.55 (d, 1H, Ar-H), 4.17 (t, 2H, CH₂-N), 2.81 (t, 4H, CH₂-CN + CH₂), 2.45 (t, 2H, CH₂), 2.17 (m, 2H, CH₂). GC/MS = 188 [M+H]⁺. Anal. Calcd. for C₁₁H₁₂N₂O (188.226): C, 70.19; H, 6.43; N, 14.88. Found: C, 70.27; H, 6.66, N, 15.07.

3-(4-Oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)propanoic acid (10). A suspension of 3-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)propanenitrile 9 (1.81 g, 9.6 mmol) in a solution of KOH pellets (0.65 g, 11.6 mmol) in water (15 mL) was heated under reflux for 1 h. The clear solution was poured in ice-cold water and then neutralized with 2N HCl. The white precipitate formed was filtered and washed with water. After recrystallization from ethanol-water the desired compound 10 was obtained in 71%; mp 155-158 °C; Rf = 0.25 (Ethyl Acetate); IR (nujol) ν cm⁻¹ = 1725 (C=O), 1700 (C=O), 1610 (C=C). NMR data: δH (CDCl₃ + DMSO-d₆) 6.67 (d, 1H, Ar-H), 6.43 (d, 1H, Ar-H), 4.14 (t, 2H, CH₂-N), 2.80 (t, 2H, CH₂), 2.72 (t, 2H, CH₂), 2.42 (t, 2H, CH₂), 2.15 (m, 2H, CH₂). GC/MS = 207 [M+H]⁺. Anal. Calcd. for C₁₁H₁₃NO₃ (207.226): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.91; H, 6.35, N, 6.48.

2,3,6,7-Tetrahydro-1H-pyrrolo[1,2-a]indole-1,8(5H)-dione (3b). A magnetically stirred mixture of 3-(4-oxo-4,5,6,7-tetrahydro-1H-indol-1-yl)propanoic acid 10 (0.25 g, 1.2 mmol) and 84% PPA (2.5 g) was heated at 90 °C for 2.5 h. After cooling the the solvent was removed in vacuo and the crude product was purified by flash column chromatography on silica gel (eluent: CH₂Cl₂/MeOH 9:1) to obtain the desired compound 3b as an yellow solid (85%), mp 175-177 °C; Rf = 0.5 (CHCl₃/MeOH 9:1); IR (nujol) ν cm⁻¹ = 1725 (C=O), 1700 (C=O), 1610 (C=C). NMR data: δH (CDCl₃) 7.05 (s, 1H, Ar-H), 4.24 (t, 2H, NCH₂), 3.12 (t, 2H, CH₂), 2.84 (t, 2H, CH₂), 2.54 (t, 2H, CH₂), 2.21 (m, 2H, CH₂); δC (CDCl₃) 194.5 (C=O), 189.7 (C=O), 143.5 (C-9a), 126.9 (C-4a), 104.5 (C-9), 104.0 (C-9a), 40.4 (C-3), 38.9 (C-2), 38.1 (C-7), 23.1 (C-5), 21.4 (C-6). GC/MS = 189 [M+H]⁺. Anal. Calcd. for C₁₁H₁₁NO₂ (189.211): C, 69.83; H, 5.86; N, 7.40. Found: C, 69.71; H, 5.80, N, 7.52.

1,2,3,5,6,7-Hexahydro-8H-pyrrolo[1,2-a]indol-8-one (11). In a flask fitted with a Dean Stark apparatus to a solution of crushed KOH pellets (1.19 g, 21.2 mmol) in 15 mL of diethylene glycol, were added in the order 2,3,6,7-Tetrahydro-1H-pyrrolo[1,2-a]indole-1,8(5H)-dione 3b (0.20 g, 1.06 mmol) and 98% hydrazine hydrate (0.53 g, 5.1 mL, 10.6 mmol). After refluxing
for one and half hours, the Dean-Stark was removed and the temperature allowed to rise to 195 °C, when refluxing was continued for additional four hours. After cooling, the solution was diluted with water and acidified with 6 N hydrochloric acid. Then the solution was extracted with dichloromethane and the organic extract washed with water. After evaporation of the solvent, the residue was purified by flash column chromatography on silica gel (Ethyl Acetate/Petroleum Ether/ 7:3) to obtain 11 as a brown solid (22%), mp 55-57 °C; Rf = 0.39 (Ethyl Acetate/Petroleum Ether/ 7:3); IR (nujol) ν cm⁻¹ = 1690 (C=O). NMR data: δH (CDCl3) 6.18 (s, 1H, Ar-H), 3.84 (t, 2H, NCH2), 2.82 (t, 2H, CH2), 2.72 (t, 2H, CH2), 2.56-2.42 (m, 4H, CH2 x 2), 2.23-2.15 (m, 2H, CH2). GC/MS = 175 [M+H]+. Anal. Calcd. for C11H13NO (175.277): C, 75.40; H, 7.48; N, 7.99. Found: C, 75.56; H, 7.41, N, 8.24.

(1E/Z,8E/Z)-2,3,6,7-Tetrahydro-1H-pyrrolo[1,2-a]indole-1,8(5H)-dione dioxime (12). A mixture of 3b (0.15 g, 0.79 mmol) with hydroxylamine hydrochloride (0.33 g, 4.74 mmol) in 6 mL of ethanol-water (in ratio of 2:1) in the presence of sodium acetate (0.78 g, 9.48 mmol) was refluxed for 6 h. On cooling, a crystalline solid was separated and, after recrystallization from ethanol-water, afforded the desired compound 12 (as a mixture of E/Z isomers) as yellow crystals (46%), mp 235 (dec.) °C; Rf = 0.47, 0.40, 0.36 (CHCl3/MEOH 9:1); IR (nujol) ν cm⁻¹ = 3150 (OH), 1670 (C=N), 1630 (C=C). NMR data: δH (CDCl3 + DMSO-d6) 10.55 (bs, 1H, OH), 10.48 (s, 1H, OH), 10.31 (bs, 1H, OH), 10.17 (s, 1H, OH), 10.12 (s, 1H, OH), 8.05 (s, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 6.66 (s, 1H, Ar-H), 4.25-4.03 (m, 6H, NCH 2 x 3), 3.18-3.05 (m, 16H, CH2 x 8), 2.48-2.59 (m, 2H, CH2), 2.07-1.81 (m, 6H, CH2 x 3). GC/MS = 219 [M+H]+. Anal. Calcd. for C11H13N3O2 (219.240): C, 60.26; H, 5.98; N, 19.17. Found: C, 60.41; H, 6.15, N, 19.26.

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References