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A new course of the Perkin cyclization of 2-(2-formyl-6-methoxyphenoxy)-alkanoic acids. Synthesis of 2-alkyl-7-methoxy-5-nitrobenzo[*b*]furans

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ABSTRACT

2-Alkyl-7-methoxy-5-nitrobenzo[*b*]furan, 2-alkyl-9-methoxy-7-nitro-3-oxo-2,3-dihydro-5*H*-benzo[*e*][1,4]-dioxepin-5-yl acetate and 2-alkyl-5-hydroxy-9-methoxy-7-nitro-5*H*-benzo[*e*][1,4]-dioxepin-3-one were formed as a result of the cyclization of 2-(2-formyl-6-methoxy-4-nitrophenoxy)alkanoic acids under classical Perkin reaction conditions. The products were characterized by spectroscopic methods and the mechanism of the cyclization is discussed.

1. Introduction

2-Formylphenoxy alkanoic acids and their derivatives are well known as bifunctional compounds, which are used in syntheses of heterocyclic structures such as benzo[*b*]furan[1] and 1,4-benzoxazepine.[2]

A number of methods exist for the synthesis of benzo[*b*]furans, and they vary in complexity and starting materials. In almost all cases, the benzo[*b*]furan synthesis is based on the cyclization of various acyclic precursors.[3] The most famous method is developed via 2-ethynylphenols.[4] On the other hand, the method via 2-(2-formylphenoxy)alkanoic acids appears practical and general for the synthesis of 2-alkylbenzo[*b*]furans using starting materials that are commercially available, and involves simple procedures. This process has been the subject of recent patents.[5] Although the synthesis of 2-benzo[*b*]furans via cyclization of 2-formylphenoxy-acetic acid has been known for a long time, there is in the literature only one attempt to explain the mechanism of the cyclization.[1f] The proposed mechanism, involving a series of rearrangements, depends upon intramolecular [2+2] ketene cycloaddition with an aldehyde.

This work presents the results of our studies on the cyclization of 2-(2-formyl-6-methoxy-4-nitrophenoxy)alkanoic acids to 2-alkyl-7-methoxy-5-nitrobenzo[*b*]furans, the latter compounds being intermediates in the synthesis of 2-alkyl-5-amino-7-methoxy-benzo[*b*]furans. Bis-*N*,*N*-dichloroethyl derivatives of such amino-benzofurans may be potential antitumour agents.

2. Results and discussion

2-(2-Formyl-6-methoxy-4-nitrophenoxy)alkanoic acids **1a–c** desired for cyclization were prepared by a known method starting from 2-hydroxy-3-methoxy-5-nitrobenzaldehyde and the corresponding methyl 2-bromo alkanoates. 2-Hydroxy-3-methoxy-5-nitrobenzaldehyde was prepared in our laboratory by nitration of *o*-vanillin with concentrated nitric acid in acetic acid solution. The reaction time and temperature were so matched that the desired 2-hydroxy-3-methoxy-5-nitrobenzaldehyde was formed in a yield of 80%. Methyl 2-bromobutanoate, -pentanoate and -hexanoate were obtained by the method described,[6] starting from a suitable carboxylic acid by chlorination with thionyl chloride, followed by bromination with bromine and esterification with methanol. All these reactions were carried out as a continuous, one-pot process and the yield of esters was over 90%. O-Alkylation of 2-hydroxy-3-methoxy-5-nitrobenzaldehyde with 2-bromoesters was made in DMF solution in the presence of potassium carbonate to give methyl 2-(2-formyl-6-methoxy-4-nitrophenoxy)alkanoate practically in quantitative yields (Scheme 1). The key problem, effectively solved, was the hydrolysis of the esters to the corresponding acids. When hydrolysis of the esters was carried out with 5% sodium hydroxide at room temperature, it gave the corresponding acid and the product of ether bond cleavage. It has been found that the unfavourable bond cleavage can be considerably restricted provided the ester hydrolysis is carried out at a temperature not exceeding 10 °C. In these conditions suitable acids **1a–c** were obtained in good yields as colourless crystals.

In order to prepare 2-alkyl-7-methoxy-5-nitrobenzo[*b*]furans **2a–c**, thoroughly dried 2-(2-formylo-6-methoxy-4-nitrophenoxy)-alkanoic acids **1a–c** were subjected to cyclization under the same

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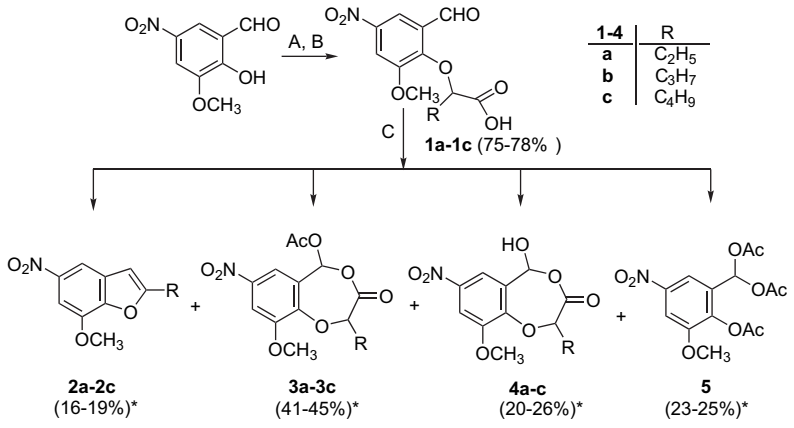


Scheme 1.

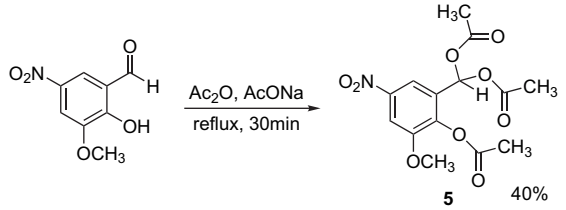
conditions applied earlier to the synthesis of 2-alkyl-5-nitrobenzo[*b*]furans,[7] i.e., in a mixture of acetic anhydride and acetic acid at reflux in the presence of anhydrous sodium acetate. The crude neutral product was analyzed by GC/MS and was found to contain four products, i.e., 2-alkyl-7-methoxy-5-nitrobenzo[*b*]furans (**2a**–**c**), 2-alkyl-9-methoxy-7-nitro-3-oxo-2,3-dihydro-5*H*-benzo[*e*]-[1,4]-dioxepin-5-yl acetates (**3a**–**c**), 2-alkyl-5-hydroxy-9-methoxy-7-nitro-5*H*-benzo[*e*][1,4]-dioxepin-3-ones (**4a**–**c**) and 2-hydroxy-3-methoxy-5-nitrobenzaldehyde triacetate (**5**) (Scheme 1).

Products **2a**–**c**, **3a** and **4a** were isolated from the mixture and their structures were established by spectroscopic methods. The other compounds **3b**,**c** and **4b**,**c** were identified by GC/MS.

The structure of **3a** was determined using ^{1}H and ^{13}C NMR spectroscopy including ^{1}H–^{13}C 2D-COSY spectra. In the ^{1}H NMR spectrum, a singlet with chemical shift δ=2.37, characteristic of CH_3 protons was detected for the acetyl groups O–CO–CH_3. A broad strong absorption band at ν=1810 cm^{-1} in the IR spectrum of **3a** is characteristic of valency bond vibrations of the carbonyl group in lactones, and a strong band at 1780 cm^{-1} corresponded to the acetate carbonyl group. In the IR spectrum of **4a** a broad band of OH group at 3500–3350 cm^{-1} and carbonyl group in lactones at 1810 cm^{-1} were present.

GC/MS analysis shows that the retention time and fragmentation of compounds **5** correspond to the retention time and fragmentation of the product obtained when 2-hydroxy-3-methoxy-5-nitrobenzaldehyde was heated for 30 min with acetic anhydride and anhydrous sodium acetate (Scheme 2). The structure of triacetate **5** was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

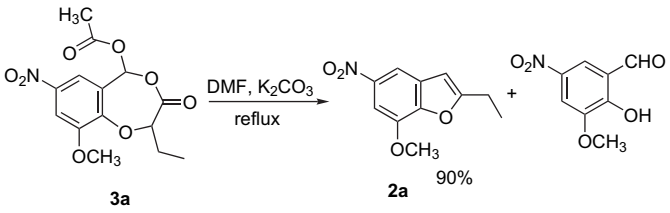
The presence of product **5** in the mixture after cyclization of acid **1a** proves that during the reaction there takes place an undesirable ether bond cleavage to form the starting benzaldehyde, which then reacts with acetic anhydride to give a triacetate. The presence of the nitro group in position **5** of the benzene ring accounts for the ease of the ethereal bond cleavage both in alkaline and acidic media.[7a]



Scheme 2.

It is known that aldehydes react with anhydrides under acid catalysis to give geminal diacetates (acylals).[8a,b] The formation of the geminal diacetates from aldehydes and acetic anhydride using strong protic acids is one of the known methods of carbonyl group protection.[8b]

Next we have found that when **3a** was heated in DMF with anhydrous potassium carbonate at 145–150 °C, benzo[*b*]furan **2a** as the main product and certain amounts of initial benzaldehyde were formed (Scheme 3).



Scheme 3.

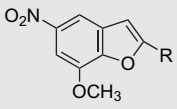
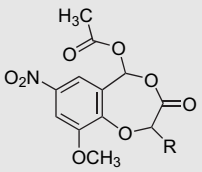
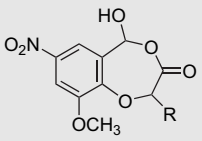
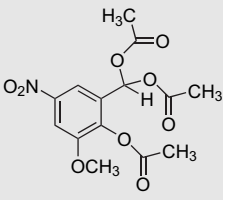
In order to obtain the desired benzo[*b*]furans in good yield, optimization of the cyclization process of model **1a** was performed changing the proportions of acetic anhydride, acetic acid in relation to acid **1a**, as well as reaction time. It was found that the highest yield of benzo[*b*]furan **2a** with an inconsiderable amount of 1,4-benzodioxepin-3-ones **3a** and **4a** could be achieved when kept for 3–3.5 h in a medium of solely acetic anhydride. When the reaction was carried out in a mixture of acetic anhydride and acetic acid, the amounts of **3a** and **4a** increased with the concentration of acetic acid.

Under the optimal conditions established for **1a**, cyclization of acids **1b** and **1c** gave the desired benzo[*b*]furans **2b** and **2c** with 62–75% GC yield (Table 1).

It is noteworthy that products **3a**–**c** and **4a**–**c** were formed in all the reaction samples, even in those where acetic acid was not added. However, such a product was not detected in any of the 2-(2-formylphenoxy)alkanoic acids, the acids being subjected to cyclization carried out in conditions identical both for the acids non-substituted on the benzene ring and those containing halogen or nitro group on position 5 of the ring.[7a,b]

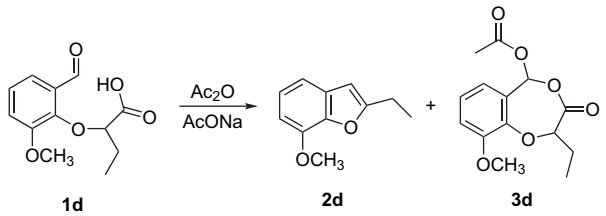
Accordingly, the outcome of cyclization tests made in this work was decidedly affected by the presence of a spatially large methoxy group in the position *ortho* to the carboxyalkylethereal grouping.

Table 1
Cyclization of 2-(2-formyl-6-methoxy-4-nitrophenoxy)alkanoic acids under optimal conditions

Starting acid **1**	Product[a] [%]			
	 **2**	 **3**	 **4**	 **5**
a	64 (44)	16 (9)	11 (6)	9
b	62 (41)	28	4	6
c	75 (49)	10	9	6

Values in brackets denote isolated yields.
[a] Relative percentage of the compounds based on the GC/MS chromatographic area.

In order to confirm the effect of the methoxy group in position *ortho* to the ethereal linkage, some cyclization reactions of 2-(2-formyl-6-methoxyphenoxy)butanoic acid **1d** in acetic anhydride and in the presence of sodium acetate were carried out. The reaction gave a mixture in which 2-ethyl-7-methoxybenzo[*b*]furan **2d** (41%) and 1,4-benzodioxapin-3-one **3d** (50%) were detected with the aid of GC/MS analysis (Scheme 4).



Scheme 4.

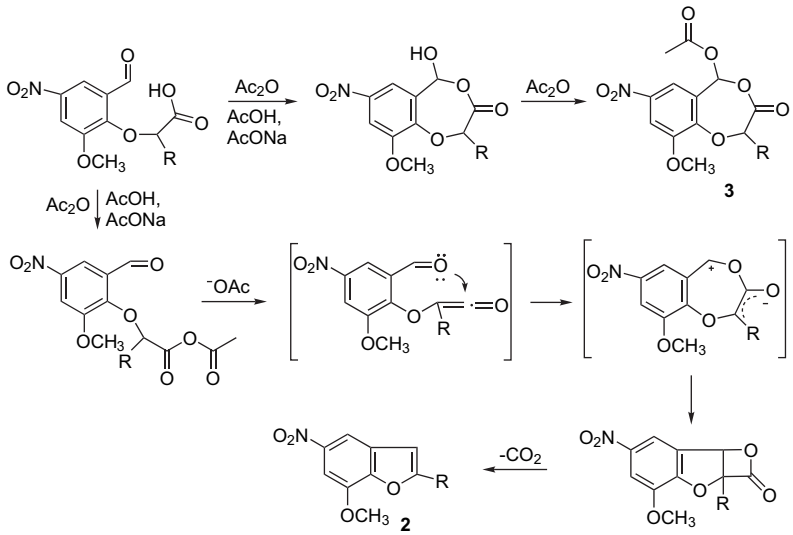
In this case, according to our expectations, the reaction mixture did not contain any product corresponding to **5**, as the cleavage of ethereal bond takes place in the presence of the electron-accepting nitro group.

The results achieved in this work give indication that cyclization of acids **1a–c**, when carried out under typical Perkin reaction conditions, i.e., in boiling acetic anhydride in the presence of sodium carbonate, it is accompanied by two concurrent processes giving rise to the formation of products **2** and **3**.

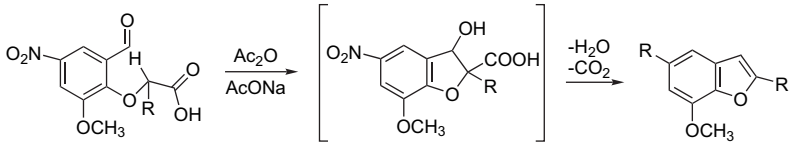
According to the mechanism proposed by the authors,[1f] the course of the first stage of 2-(2-formylphenoxy)alkanoic acid cyclization depends on reaction of the acid with acetic anhydride to give a mixed anhydride and then phenoxyketene. The above reaction is followed by a two-step intramolecular [2+2] cycloaddition via a dipolar intermediate, which undergoes ring closure to the β-lactone. Subsequent decarboxylation in acetic anhydride at reflux yields the substituted benzo[*b*]furan **2**.[1f]

A competitive process leading to product **3** is an intermolecular acylation of the aldehyde group, similar to the formation of acylals using anhydrides or acids.[8a] An intermolecular acylation first forms a hemiacylal, which enters into reaction with acetic anhydride and brings about a mixed diacylal **3** (Scheme 5). This process is favoured by the presence of a spatially large methoxy group placed in a position *ortho* to alkoxyalkylcarboxyl chain of acids **1a–c**. This fact makes most of the atoms exist in a conformation where the aldehyde and acid groups are neighbouring, which may give effect to intermolecular acylation and the consequent production of a hemiacylal.

One can assume an optional formation of 7-member acetate **3a–c**, formed from a mixed anhydride brought about by the reaction of starting acids **1a–c** with acetic acid, followed by intermolecular



Scheme 5.



Scheme 6.

cyclization. Considering the results achieved by Kochhar,[8a] the mechanism of conversion of aldehydes into geminal diacetates involves an intermolecular transfer of the second acetate group after the initial attack by acetic anhydride. Such a mechanism seems probable, since there first takes place an intermolecular reaction of the carboxyl group with the aldehyde, leading to a hemiacylal and afterwards by acetylation to product **3**. The deposition of hemiacylal failed, but its presence was found in almost all reactions by GC/MS analysis.

Regarding the cyclization results achieved in this work, the mechanism of benzo[*b*]furan formation through formation of a mixed anhydride in the first stage is more probable than its alternative depending on cyclization by intramolecular aldolization (Scheme 6).[3b] The methoxyl group in position *ortho* to ethereal bond in formyl acid should then affect the aldolization to the same extent and cause increase in the yield of benzo[*b*]furan and formation of product **3**.

The presence of acetic acid in the reaction mixture hinders the production of the mixed anhydride, therefore in the cyclization tests made in the presence of acetic acid, there appears to be a higher competitive process of seven-member ring formation, and for the acids with a nitro group, also a higher participation of the product in the decomposition of the ethereal bond **5** can be observed.

3. Summary

We have found a new course of cyclization of 2-(2-formyl-6-methoxy-4-nitrophenoxy)alkanoic acids under typical Perkin reaction conditions. The cyclization brings about, beside benzo[*b*]-furan, a seven-member lactone ring of 1,4-benzodioxepin-3-one. Optimal conditions of the cyclization have been determined, giving rise to benzo[*b*]furan with good yield.

4. Experimental section

^{1}H and ^{13}C NMR spectra were recorded on a TM Bruker DPX 400 instrument as solutions in $CDCl_3$. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for ^{1}H NMR, and $CDCl_3$ (77.0 ppm) for ^{13}C NMR. Mass spectra were obtained on an Agilent Technologies 6890 N apparatus, equipped with mass detector 5973 Network and 30 m×0.2 mm capillary column filled up with 0.25 μm film of a 5% MePh silicate. IR spectra were recorded on a Specord M 80 Carl Zeiss spectrophotometer. All melting points were determined using a Boetius apparatus and are uncorrected.

2-Hydroxy-3-methoxy-5-nitrobenzaldehyde (mp 140–142 °C) was obtained by nitration of 2-hydroxy-3-methoxybenzaldehyde (*o*-vanilin), with 100% nitric acid in acetic solution, although it is commercially available. Methyl 2-bromoalkanoates, -butanoate, -pentanoate and -hexanoate, were obtained according to the literature.[6] All other reagents and solvents were commercially available, >98% purity, and used without further purification.

4.1. Synthesis of 2-(2-formyl-6-methoxy-4-nitrophenoxy)-butanoic acid (1a)

A mixture of 2-hydroxy-3-methoxy-5-nitrobenzaldehyde (9.9 g, 0.05 mol), methyl 2-bromobutanoate (9.1 g, 0.05 mol), anhydrous potassium carbonate (6.9 g, 0.05 mol) and dry DMF (90 mL) was heated at 93–95 °C with stirring for 4 h. Then the solution was poured into ice-water, the precipitate was filtered off, washed with water and dried in air. The crude ester was recrystallized from methanol/water 2:1 to give pale beige crystals, mp 103–105 °C (lit.[2c] 103–105 °C). The mixture of the ester and 5% sodium hydroxide was stirred magnetically at 10 °C for 2 h. The solution was filtered through Celite, the filtrate was acidified with 5% hydrochloric acid and the precipitate was isolated. The crude product was recrystallized from 2:1 methanol/water, to give **1a** as colourless crystal (11.1 g, 78%), mp 149–151 °C.

GC/MS (MeOH), **1a** methyl ester, MS *m*/*z*: 297 (M^+, 32%), 280 (1%), 265 (16%), 251 (1%), 238 (77%), 225 (3%), 212 (20%), 196 (100%), 181 (16%), 167 (12%), 151 (56%), 136 (13%), 122 (14%), 101 (22%), 79 (7%), 59 (45%). ^{1}H NMR δ 10.53 (s, 1H, CHO), 10.40 (s, 1H, COOH), 8.30 (d, *J*=2.6, 1H, Ar), 7.94 (d, *J*=2.6, 1H, Ar), 5.31–5.28 (m, 1H, CH), 3.98 (s, 3H, OCH_3), 2.19–2.04 (m, 2H, CH_2), 1.15 (t, *J*=7.4, 3H, CH_3); ^{13}C NMR δ 188.8, 176.3, 153.9, 151.8, 143.5, 128.9, 115.7, 111.8, 80.5, 56.7, 26.3, 9.3. IR (KBr) ν: 3550–3350, 1740–1720, 1695, 1530 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_7$ (283.07): C, 50.89; H, 4.63; N, 4.95. Found: C, 50.77; H, 4.71; N, 5.01.

4.2. Synthesis of 2-(2-formyl-6-methoxy-4-nitrophenoxy)-pentanoic acid (1b)

Starting from 2-hydroxy-3-methoxy-5-nitrobenzaldehyde (9.9 g, 0.05 mol), methyl 2-bromopentanoate (9.8 g, 0.05 mol), potassium carbonate (6.9 g, 0.05 mol) and DMF (90 mL) the same procedure was followed as described for compound **1a**, to give **1b** as colourless crystals (11.3 g, 76%), mp 125–127 °C.

GC/MS (MeOH), **1b** methyl ester, MS *m*/*z*: 311 (M^+, 18%), 267 (24%), 252 (11%), 238 (41%), 221 (6%), 206 (100%), 192 (10%), 177 (7%), 160 (12%), 135 (11%), 119 (9%), 106 (4%), 91 (3%), 77 (5%), 55 (7%). ^{1}H NMR δ 10.52 (s, 1H, CHO), 9.10 (s, 1H, COOH), 8.30 (d, *J*=2.6, 1H, Ar), 7.93 (d, *J*=2.6, 1H, Ar), 5.33 (t, *J*=5.9, 1H, CH), 3.98 (s, 3H, OCH_3), 2.06–2.01 (m, 2H, CH_2), 1.67–1.57 (m, 2H, CH_2), 1.02 (t, *J*=7.4, 3H, CH_3); ^{13}C NMR δ 188.8, 176.4, 153.9, 151.8, 143.5, 128.9, 115.6, 111.7, 79.4, 56.6, 34.9, 18.2, 13.7. IR (KBr) ν: 3500–3350, 1740–1725, 1700, 1530 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_7$ (297.08): C, 52.53; H, 5.09; N, 4.71. Found: C, 52.45; H, 5.19; N, 4.75.

4.3. Synthesis of 2-(2-formyl-6-methoxy-4-nitrophenoxy)-hexanoic acid (1c)

Starting from 2-hydroxy-3-methoxy-5-nitrobenzaldehyde (9.9 g, 0.05 mol), methyl 2-bromohexanoate (10.5 g, 0.05 mol), potassium carbonate (6.9 g, 0.05 mol) and DMF (90 mL) the same procedure was followed as described for compound **1a**, to give **1c** as beige crystals (11.7 g, 75%), mp 128–130 °C.

GC/MS (MeOH), **1c** methyl ester, MS *m*/*z*: 325 (M^+, 13%), 281 (18%), 266 (7%), 252 (9%), 238 (27%), 221 (4%), 206 (100%), 182 (9%), 160 (8%), 135 (9%), 119 (6%), 106 (2%), 91 (2%), 69 (3%), 55 (4%). ^{1}H NMR δ 10.53 (s, 1H, CHO), 8.32 (d, *J*=2.6, 1H, Ar), 8.11 (br band, 1H, COOH), 7.94 (s, 1H, Ar), 5.32 (t, *J*=5.1, 1H, CH), 3.98 (s, 3H, OCH_3), 2.04 (t, *J*=6.2, 2H, CH_2), 1.52–1.59 (m, 2H, CH_2), 1.42 (t, *J*=6.5, 2H, CH_2), 0.95 (t, *J*=7.1, 3H, CH_3); ^{13}C NMR δ 188.8, 176.1, 153.9, 151.8, 143.5, 128.9, 115.8, 111.7, 79.6, 56.6, 32.7, 26.9, 22.3, 13.9. IR (KBr)

ν: 3500–3300, 1740–1720, 1700, 1530 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_7$ (311.10): C, 54.02; H, 5.50; N, 4.50. Found: C, 53.91; H, 5.63; N, 4.57.

4.4. Synthesis of 2-(2-formyl-6-methoxyphenoxy)butanoic acid (1d)

Starting from 2-hydroxy-3-methoxybenzaldehyde (7.6 g, 0.05 mol), methyl 2-bromobutanoate (9.1 g, 0.05 mol), potassium carbonate (6.9 g, 0.05 mol) and DMF (90 mL) the same procedure was followed as described for compound **1a**. The ester was hydrolyzed by heating with 5% KOH on a boiling water bath for 2.5 h, to give **1d** as pale beige crystals (8.9 g, 75%), mp 112–113 °C (lit.[1f] 113–114.5 °C).

GC/MS, MS *m/z*: 238 (M^+, 21%), 220 (1%), 207 (2%), 194 (14%), 179 (2%), 165 (8%), 152 (100%), 137 (11%), 122 (18%), 106 (68%), 93 (8%), 77 (9%), 52 (6%). ^{1}H NMR δ 10.62 (s, 1H, COOH), 10.48 (s, 1H, CHO), 7.41 (t, J=4.4, 1H, Ar), 7.14 (d, J=3.9, 2H, Ar), 5.03 (t, J=5.5, 1H, CH), 3.86 (s, 3H, OCH_3), 2.10–2.01 (m, 2H, CH_2), 1.11 (t, J=7.4, 3H, CH_3).

4.5. Cyclization of 2-(2-formyl-6-methoxy-4-nitrophenoxy)-butanoic acid (1a)

To a mixture of acetic anhydride (35 mL) and sodium acetate (5.7 g, 0.07 mol), acid **1a** (1.98 g, 0.007 mol) was added. The mixture was stirred and heated at reflux for 3.5 h. After it was poured into ice-water the precipitate was filtered. The crude product was dissolved in methylene chloride, treated with 5% sodium bicarbonate and water. The organic layer was dried, evaporated and the residue crude analyzed by GC/MS. The brown solid was recrystallized from methanol to yield pure **2a** (0.66 g, 44%) as a beige solid. After methanol was removed from the filtrate on a rotary evaporator, the residue was recrystallized from chloroform/hexane 1:3 to first yield colourless crystals, identified as **3a** (0.21 g, 9%) and secondly a pale yellow semisolid **4a** (0.12 g, 6%).

*4.5.1. 2-Ethyl-7-methoxy-5-nitrobenzo[b]furan (**2a**)*

Mp 98–100 °C, GC/MS, MS *m/z*: 221 (M^+, 100%), 206 (36%), 191 (5%), 175 (45%), 160 (19%), 145 (4%), 131 (5%), 115 (14%), 91 (7%), 77 (6%), 63 (4%), 50 (2%). ^{1}H NMR δ 8.07 (d, J=2.0, 1H, Ar), 7.66 (d, J=2.0, 1H, Ar), 6.51 (s, 1H, Ar), 4.08 (s, 3H, OCH_3), 2.87–2.85 (m, 2H, CH_2), 1.39–1.35 (m, 3H, CH_3); ^{13}C NMR δ 164.3, 146.9, 144.5, 144.5, 129.9, 109.8, 102.4, 101.2, 56.5, 21.8, 11.7. IR (KBr) ν: 3110, 2980, 2930, 1600, 1590, 1530, 1430, 1335, 1325 cm^{-1}. Anal. Calcd for $C_{11}H_{11}NO_4$ (221.07): C, 59.73; H, 5.01; N, 6.33. Found: C, 59.61; H, 5.13; N, 6.37.

*4.5.2. 2-Ethyl-3,5-dihydro-9-methoxy-7-nitro-3-oxo-2H-benzo[e][1,4]dioxepin-5-yl acetate (**3a**)*

Mp 107–107.5 °C, GC/MS, MS *m/z*: 325 (M^+, 1%), 297 (2%), 283 (27%), 239 (5%), 222 (2%), 197 (100%), 180 (5%), 167 (3%), 151 (12%), 136 (3%), 122 (3%), 108 (2%), 92 (1%), 79 (2%), 63 (2%), 50 (1%). ^{1}H NMR δ 8.11 (s, 1H, Ar), 7.92 (s, 1H, Ar), 6.53 (s, 1H, CH), 4.43 (br s, 1H, CH), 3.96 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3), 2.07–2.04 (m, 1H, CH_2), 1.94–1.88 (m, 1H, CH_2), 1.10 (t, J=7.4, 3H, CH_3); ^{13}C NMR δ 171.8, 167.1, 152.2, 146.1, 143.7, 129.5, 114.1, 108.9, 97.6, 76.0, 56.8, 24.1, 20.4, 9.2. IR (KBr) ν: 3000–2900, 1810, 1780, 1545, 1200–1180 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_8$ (325.08): C, 51.70; H, 4.65; N, 4.31. Found: C, 51.40; H, 4.40; N, 4.21.

*4.5.3. 2-Ethyl-5-hydroxy-9-methoxy-7-nitro-5H-benzo[e][1,4]-dioxepin-3-one (**4a**)*

GC/MS, MS *m/z*: 283 (M^+, 27%), 239 (5%), 222 (2%), 197 (100%), 180 (5%), 167 (3%), 151 (12%), 136 (3%), 122 (3%), 108 (2%), 93 (1%), 79 (2%), 59 (2%). ^{1}H NMR δ 8.04 (s, 1H, Ar), 7.90 (s, 1H, Ar), 6.65 (d, J=5.2, 1H, CH), 4.10 (br s, 1H, CH), 3.97 (s, 3H, OCH_3), 2.92 (br s, 1H, OH), 2.06–2.03 (m, 1H, CH_2), 1.92–1.88 (m, 1H, CH_2), 1.11 (t, J=7.4, 3H, CH_3); ^{13}C NMR δ 171.3, 152.0, 146.0, 143.4, 129.1, 114.0, 108.8, 94.8, 78.2, 56.4, 24.0, 9.0. IR (KBr) ν: 3550–3350, 3000–2850, 1810, 1540, 1170 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_7$ (283.07): C, 50.89; H, 4.63; N, 4.95. Found: C, 50.75; H, 4.69; N, 5.03.

4.6. Cyclization of 2-(2-formyl-6-methoxy-4-nitrophenoxy)-pentanoic acid (1b)

Starting from acid **1b** (2.08 g, 0.007 mol), acetic anhydride (35 mL) and sodium acetate (5.7 g, 0.07 mol) following a similar procedure to that described for **1a** yielded pure **2b** as a beige solid (0.68 g, 41%). Compounds **3b** and **4b** were identified in the crude reaction mixture by GC/MS analysis.

*4.6.1. 2-Propyl-7-methoxy-5-nitrobenzo[b]furan (**2b**)*

Mp 72–74 °C, GC/MS, MS *m/z*: 235 (M^+, 87%), 220 (1%), 206 (100%), 189 (17%), 174 (3%), 160 (49%), 145 (5%), 131 (3%), 117 (17%), 103 (3%), 89 (7%), 76 (3%), 63 (4%), 50 (1%). ^{1}H NMR δ 8.07 (s, 1H, Ar), 7.66 (s, 1H, Ar), 6.51 (s, 1H, Ar), 4.08 (s, 3H, OCH_3), 2.79 (t, J=7.4, 2H, CH_2), 1.83–1.78 (m, 2H, CH_2), 1.02 (t, J=7.3, 3H, CH_3); ^{13}C NMR δ 162.8, 146.9, 144.5, 144.5, 129.9, 109.8, 103.2, 101.2, 56.5, 30.3, 20.9, 13.7. IR (KBr) ν: 3110–2920, 1600, 1590, 1530, 1425, 1340, 1320 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_4$ (235.08): C, 61.27; H, 5.57; N, 5.95. Found: C, 61.18; H, 5.63; N, 5.99.

*4.6.2. 2-Propyl-3,5-dihydro-9-methoxy-7-nitro-3-oxo-2H-benzo[e][1,4]dioxepin-5-yl acetate (**3b**)*

GC/MS, MS *m/z*: 339 (M^+, 1%), 311 (2%), 297 (19%), 252 (2%), 239 (5%), 224 (1%), 197 (100%), 180 (5%), 167 (3%), 151 (10%), 136 (3%), 122 (2%), 101 (2%), 83 (2%), 69 (1%), 55 (4%).

*4.6.3. 2-Propyl-5-hydroxy-9-methoxy-7-nitro-5H-benzo[e][1,4]dioxepin-3-one (**4b**)*

GC/MS, MS *m/z*: 297 (M^+, 19%), 252 (2%), 239 (5%), 224 (1%), 197 (100%), 180 (5%), 167 (3%), 151 (10%), 136 (3%), 122 (2%), 101 (2%), 83 (2%), 69 (1%), 55 (4%).

4.7. Cyclization of 2-(2-formyl-6-methoxy-4-nitrophenoxy)-hexanoic acid (1c)

Starting from acid **1c** (2.18 g, 0.007 mol), acetic anhydride (35 mL) and sodium acetate (5.7 g, 0.07 mol) following a similar procedure to that described for **1a** yielded pure **2c** as a beige solid (0.83 g, 49%). Compounds **3c** and **4c** were identified in the crude reaction mixture by GC/MS analysis.

*4.7.1. 2-Butyl-7-methoxy-5-nitrobenzo[b]furan (**2c**)*

Mp 45–47 °C, GC/MS, 249 (M^+, 78%), 234 (3%), 220 (2%), 206 (100%), 190 (9%), 174 (4%), 160 (50%), 145 (4%), 131 (3%), 117 (12%), 103 (4%), 89 (7%), 76 (3%), 63 (3%), 50 (1%). ^{1}H NMR δ 7.99 (s, 1H, Ar), 7.59 (s, 1H, Ar), 6.43 (s, 1H, Ar), 4.00 (s, 3H, OCH_3), 2.75 (d, J=6.6, 2H, CH_2), 1.68 (t, J=6.5, 2H, CH_2), 1.35 (d, J=6.8, 2H, CH_2), 0.89 (d, J=6.6, 3H, CH_3); ^{13}C NMR δ 163.1, 146.9, 144.5, 129.9, 109.8, 103.1, 101.2, 56.5, 29.6, 28.1, 22.3, 13.8. IR (KBr) ν: 3120–2890, 1600, 1590, 1530, 1425, 1335, 1325 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_4$ (249.10): C, 62.64; H, 6.07; N, 5.62. Found: C, 62.53; H, 6.15; N, 5.69.

*4.7.2. 2-Butyl-3,5-dihydro-9-methoxy-7-nitro-3-oxo-2H-benzo[e][1,4]dioxepin-5-yl acetate (**3c**)*

GC/MS, MS *m/z*: 353 (M^+, 1%), 325 (2%), 311 (14%), 281 (1%), 266 (2%), 252 (1%), 239 (5%), 197 (100%), 181 (4%), 167 (3%), 151 (8%), 136 (2%), 115 (2%), 97 (2%), 83 (1%), 69 (4%), 55 (2%).

*4.7.3. 2-Butyl-5-hydroxy-9-methoxy-7-nitro-5H-benzo[e][1,4]-dioxepin-3-one (**4c**)*

GC/MS, MS *m/z*: 311 (M^+, 14%), 281 (1%), 266 (2%), 252 (1%), 239 (5%), 197 (100%), 181 (4%), 167 (3%), 151 (8%), 136 (2%), 122 (2%), 97 (2%), 83 (1%), 69 (4%), 55 (2%).

4.8. Cyclization of 2-(2-formyl-6-methoxyphenoxy)butanoic acid (1d)

Starting from acid **1d** (1.67 g, 0.007 mol), acetic anhydride (35 mL) and sodium acetate (5.7 g, 0.07 mol) following a similar procedure to that described for **1a** yielded a mixture of **2d** (41%) and **3d** (50%).

*4.8.1. 2-Ethyl-7-methoxybenzo[b]furan (**2d**)*

GC/MS, MS *m*/*z*: 176 (M^+, 100%), 161 (99%), 146 (19%), 131 (6%), 118 (15%), 103 (8%), 90 (7%), 77 (10%), 63 (5%), 50 (3%).

*4.8.2. 2-Ethyl-3,5-dihydro-9-methoxy-3-oxo-2H-benzo[e][1,4]dioxepin-5-yl acetate (**3d**)*

GC/MS, MS *m*/*z*: 280 (M^+, 59%), 238 (1%), 220 (2%), 207 (1%), 193 (23%), 176 (42%), 152 (100%), 137 (42%), 121 (11%), 106 (19%), 93 (6%), 77 (8%), 55 (4%).

4.9. Synthesis of acetic acid acetoxy-(2-acetoxy-3-methoxy-5-nitrophenyl)methyl ester (5)

A mixture of 2-hydroxy-3-methoxy-5-nitrobenzaldehyde (0.6 g, 0.003 mol), acetic anhydride (12 mL) and sodium acetate (2.5 g, 0.03 mol) was heated at reflux for 30 min. After it was poured into ice-water, the precipitate was filtered, washed with water and dried. Purification was achieved by recrystallization from methanol to yield **5** (0.35 g, 40%) as beige crystals, mp 114–116 °C.

GC/MS, MS *m*/*z*: 341 (M^+, 1%), 282 (2%), 239 (9%), 221 (3%), 197 (100%), 181 (4%), 167 (3%), 145 (8%), 122 (1%), 103 (8%), 79 (1%), 65 (1%), 51 (1%). ^{1}H NMR δ 8.14 (d, J=2.5, 1H, CH), 7.92 (s, 1H, Ar), 7.86 (d, J=2.5, 1H, Ar), 3.94 (s, 3H, OCH_3), 2.37 (s, 3H, OCH_3), 2.13 (s, 6H, OCH_3); ^{13}C NMR δ 168.2, 167.6, 152.2, 146.1, 142.9, 130.5, 114.7, 108.2, 83.9, 56.8, 20.7, 20.4. IR (KBr) ν: 1790–1770, 1545, 1370, 1345, 1235, 1200, 1170 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_9$ (341.07): C, 49.27; H, 4.43; N, 4.10. Found: C, 49.11; H, 4.53; N, 4.17.

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