Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1301–1307

TETRAHEDRON

A rapid and efficient microwave-assisted synthesis of hydantoins and thiohydantoins

Giulio G. Muccioli,[a] Jacques H. Poupaert,[a] Johan Wouters,[b,†] Bernadette Norberg,[b] Wolfgang Poppitz,[c] Gerhard K. E. Scriba[d] and Didier M. Lambert[a,*]

[a]*Laboratoire de Chimie pharmaceutique et de Radiopharmacie, Ecole de Pharmacie, Faculté de Médecine, Université catholique de Louvain, Avenue E. Mounier 73, UCL-CMFA 7340, B-1200 Bruxelles, Belgium*
[b]*Laboratoire de Chimie moléculaire structurale, Faculté des Sciences, Facultés universitaires Notre Dame de la Paix, Rue de Bruxelles, 61, 5000 Namur, Belgium*
[c]*Department of Inorganic and Analytical Chemistry, University of Jena, August-Bebel-Strasse 2, D-07743 Jena, Germany*
[d]*Department of Pharmaceutical Chemistry, University of Jena, Philosophenweg 14, D-07743 Jena, Germany.*

Received 20 September 2002; revised 18 November 2002; accepted 19 December 2002

Abstract—The present paper describes studies on the synthesis of the antiepileptic drug phenytoin, and of structurally related derivatives. First, the influence of the solvent has been investigated in the microwave-assisted synthesis of the drug, resulting in a yield improvement and a cleaner reaction. Second, a two-step reaction is described to synthesize selectively and in high yields phenytoin. The first step consists in microwave activation of the reaction of benzil with thiourea, the second step includes the conversion of the resulting 2-thiohydantoin to phenytoin using hydrogen peroxide. Moreover, microwave activation is a very convenient method for the synthesis of 3-alkylated phenytoin derivatives, resulting in a much more selective method than the previously reported procedure using alkylating agents.

1. Introduction

The imidazolidine-2,4-dione, or hydantoin nucleus, is a common 5-membered ring containing a reactive cyclic urea core. This heterocycle is present in a wide range of biologically active compounds including antiarrhytmics,[1] anticonvulsant[2] and antitumor[3] agents. Among these agents, phenytoin (**3a**, X=O), or 5,5-diphenylhydantoin, is a well-known therapeutic drug for the treatment of epileptic seizures.[4] More than 60 years since Merrit and Putnam demonstrated that phenytoin was effective against electrically induced seizures in the cat,[5] the compound is still the drug of choice for the treatment of generalised tonic–clonic seizures (so-called grand mal epilepsy) and focal motor seizures.[6] Nowadays, phenytoin has found new applications due to the neuro-and cardioprotective properties.[7,8]

Imidazolidinediones are a common template in combinatorial chemistry libraries.[9] Recently, our group initiated a medicinal chemistry research program targeting the cannabinoid receptors CB_1 and CB_2 using a phenytoin derivative as template.[10,11] Due to the growing interest of medicinal chemists in the hydantoin scaffold, we developed an efficient and rapid synthesis of phenytoin and related compounds using microwave activation. Microwave activation has received increasing interest in organic synthesis because of rapid reaction rates, increased yields and cleaner reaction conditions.[12] Recently, several 1,5-diphenyl hydantoins have been prepared by microwave-assisted synthesis.[13]

The most straightforward condition for the synthesis of phenytoin is the base-catalysed condensation using benzil (**1**) and urea (**2a**, X=O) (Scheme 1), known as the Biltz synthesis of phenytoin.[14] Dunnavant and James showed that the reaction proceeds via a benzilic rearrangement.[15] The authors also studied the optimal ratio being 1:2 in order to reduce the side product **4a**. Poupaert and co-workers previously reported[16] that the use of a two-phase system such as aqueous KOH/*n*-BuOH and PEG 600 as phase transfer catalyst drastically reduced the quantity of side-product increasing the yield of phenytoin (87–93%). The glycolureide **4a** was obtained as a single diastereomer possessing *cis* configuration.[17]

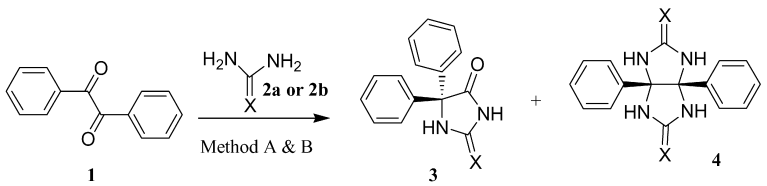
The present study reports several improvements of the Biltz reaction allowing the rapid synthesis of phenytoin and

Keywords: phenytoin; microwave activation; 5-aryl-3-alkyl-imidazolidinediones.

* Corresponding author. Tel.: +32-2-764-73-47; fax: +32-2-764-73-63; e-mail: lambert@cmfa.ucl.ac.be

† Present address: Institut de Recherches Microbiologiques Wiame—Av E Gryzon 1, 1070 Brussels, Belgium.

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00033-4



Scheme 1. Synthetic routes to diphenylhydantoin and diphenylthiohydantoin. Method A: conventional route known as Biltz's synthesis of phenytoin (**3a**) and diphenylthiohydantoin (**3b**), obtained from benzil (**1**) and urea (**2a**) or thiourea (**2b**) in absence or presence of microwave activation. Method B: two-step procedure for preparing phenytoin (**3a**) following the microwave-assisted condensation of benzile and thiourea (**2b**) giving diphenylthiohydantoin (**3b**) followed by H_2O_2 oxidation in DMF/acetic acid at room temperature.

structurally related derivatives. First, we have investigated the type of solvent in view of adapting the Biltz synthesis to microwave activation. Secondly, we have developed a two-step procedure via synthesis of the 2-thiophenytoin and subsequent conversion into phenytoin resulting in the virtual absence of the glycolureide side product **4a**. Finally, we have applied microwave activation to the synthesis of N_3-alkylated phenytoin derivatives including 2-thiophenytoin.

2. Results and discussion

2.1. Microwave activation of phenytoin synthesis

The Biltz synthesis is a common way to synthesise phenytoin (**3a**, X=O) starting from benzil and urea. Two procedures, the classical one under thermal heating and a new microwave-assisted approach, were compared using the same reacting mixtures. We used a pulsed method[18,19] for the microwave-activation in order to maximise the microwave effect and to avoid the loss of solvent and starting material due to the heating of the reaction mixture. Nine microwave pulses were applied using a household oven over a 30 min period. The time periods between pulses allowed the cooling of the mixture.

The principal limitation of the Biltz synthesis of phenytoin is the concomitant formation of **3** and **4** (Scheme 1). Under homogeneous reaction conditions, using ethanol as solvent, the yield of **3** is less than 50%. In ethanol/water mixtures the yield of pure **3a** never exceeds 55%. According to our studies the yield of isolated **4a** can be as high as 20%. Changing the strength of the base does not significantly alter the ratio of products **3a** and **4a**, but rather affects the kinetics of the reaction.[16] Thus, while the reaction has been explored regarding the stoichiometry[15] and the type of the base, to the best of our knowledge the role of the solvent has never been studied in detail previously.

Frequently, solvent systems have to be adapted in order to allow microwave-organic reaction enhancement (MORE).[20,21] Solvents useful for microwave activation

Table 1. Solvent effect (% yield) in the microwave-assisted (microwave) and the regular Biltz synthesis (thermal) of phenytoin (**3**)

Solvent	Microwave[a]	Thermal
DMSO	80	36
DMSO/H_2O[b]	76	62
Sulfolane	78	57
Sulfolane/H_2O[b]	71	58
Dioxane	45	25
Dioxane/H_2O[b]	80	58

The same composition of the reagents was used in each type of synthesis. The reaction mixture was heated for 2 h under thermal reaction conditions or submitted to nine 750 W pulses over a period of 30 min in the microwave-assisted synthesis. Reactions were carried out at the same temperature under both reaction conditions.
[a] Experiments done in triplicate.
[b] 40:100, v/v.

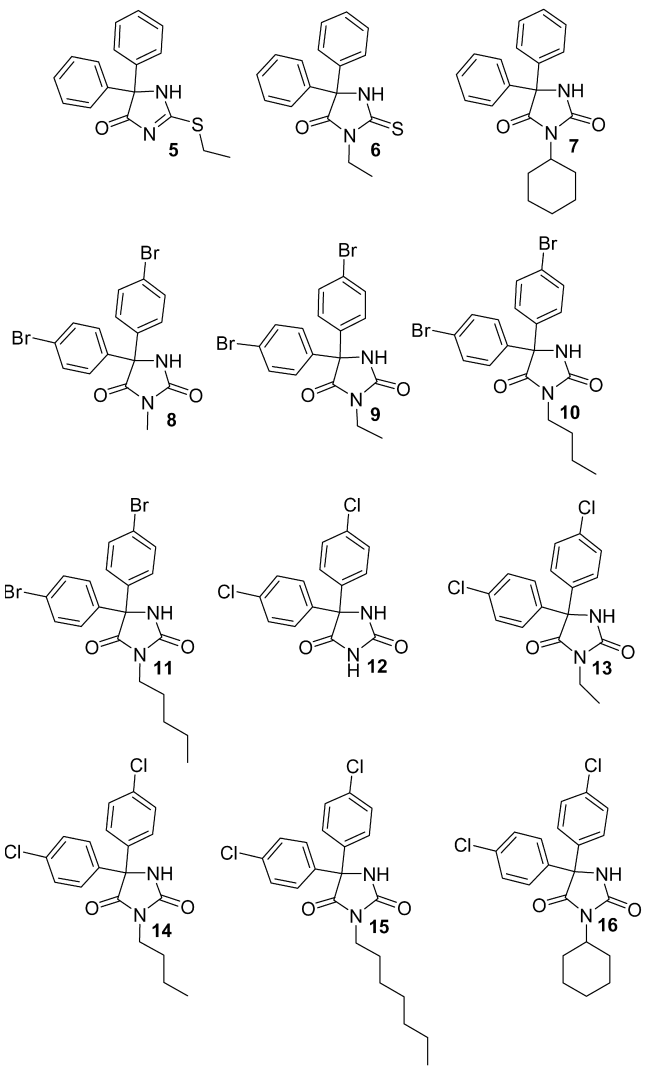
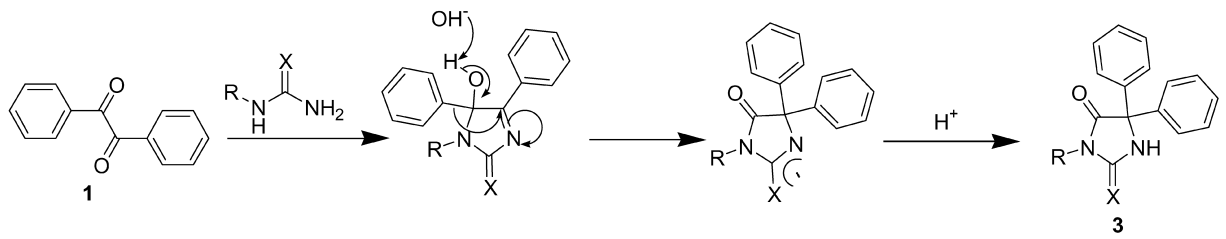


Figure 1. Structures of *S*-ethyl-5,5′-diphenyl-2-thiohydantoin (**5**), 3-alkyl-2-thiohydantoins (**6**), 3-alkyl-5,5′-di(para-substitutedphenyl)hydantoins (**7**–**16**). Excepted for compound **5**, all compounds have been prepared from benzil and alkylureas or alkylthiourea under microwave activation.



Scheme 2. Proposed mechanism of condensation of benzile and alkylurea followed by the benzylic rearrangement.

are dipolar solvents especially those with a high boiling point.[22] We first investigated solvents such as DMSO and DMF because we have obtained a yield of **3a** of up to 62% in earlier studies when using DMSO–water mixtures. Using microwave activation, with the same solvent composition and temperature (~110°C) than in the thermal reaction, the yield of **3a** was somewhat improved (76%) and a diminution in the side product (**4a**) yield was observed. In addition, the reaction was complete after 30 min instead of 2 h under classical thermal conditions. Actually, when we performed the thermal reaction under reflux for only 30 min (reacting time of the microwave-assisted reaction) nearly 50% of the starting benzil was recovered and the phenytoin yield was as low as 26%. It is noteworthy that in the microwave-assisted reaction after the first 90 s pulse, 40% of the benzil was still present and the phenytoin yield was 40% instead of 76% at the end of the pulse sequence. When the reaction was performed in DMSO under microwaves the yield of **3a** slightly increased to 80%. Similar results were obtained with sulfolane and dioxane (Table 1). However, DMF gave much lower yields. This can be explained by the extensive hydrolysis of DMF under the highly basic conditions and high temperatures which rapidly depletes the KOH concentration in the reaction mixture.

2.2. Synthesis of phenytoin via the 2-thiophenytoin

In our efforts to improve and extend the scope of the Biltz synthesis of phenytoin without microwave activation, we noticed that the reaction of benzil with thiourea in ethanolic KOH did not yield any **4b**. In addition, the presence of water in the reaction mixture increased the yield of **3b** (X=S) with a corresponding decrease of **4b**. In the microwave-assisted procedure, DMSO was chosen because of its high boiling point and solvating power. The reaction of benzil (**1**) with thiourea (**2b**, X=S) in DMSO using aqueous KOH as catalyst gave the 2-thiohydantoin derivative (**3b**, X=S) in high yield (92%). Moreover, the thioglycolureide (**4b**) was virtually absent from the reaction mixture. After precipitation, the crude product **3b** was oxidized to phenytoin (**3a**) using hydrogen peroxide in DMF/acetic acid at room temperature in good yields (95%). In conclusion, the combination of this two-step procedure and the use of microwaves allowed to obtain phenytoin in high yield and by minimal work-up.

2.3. Synthesis of phenytoin derivatives

In our studies to synthesize N_3-alkylated phenytoin derivatives, we noted that alkylation resulted, in addition to the desired N_3-alkylated derivatives, in N_1-alkyl and *O*-alkyl (or *S*-) side products often requiring tedious separation procedures to obtain pure N_3-alkylated compounds.[8] In view of obtaining a rapid and efficient synthesis of these derivatives, microwave activation has been applied to reaction mixtures containing different benzil and alkylated (thio)urea derivatives allowing us to obtain the N_3-alkyl (thio)hydantoin in a good yield. The new hydantoin derivatives **7**–**16** (Fig. 1) have been prepared from the corresponding alkylureas and either 4,4-dichlorobenzil or 4,4′-dibromobenzil. The proposed mechanism (Scheme 2) is similar to the mechanism of the classical Biltz synthesis of phenytoin.[23] The alkylurea derivatives were prepared by reaction of potassium cyanate and the corresponding alkylamines.[24] Interestingly, the microwave-assisted procedure gave easy access to 3-alkyl-2-thiohydantoin. Under alkylating conditions, treatment of **3b** (X=S) with iodoethane mainly yields the *S*-ethyl derivative **5**, while reaction of ethylthiourea gave *N*-ethyl-2-thio-phenytoin **6**. The structures of compounds **5** and **6** (Fig. 1) gave distinct ^{1}H NMR and ^{13}C NMR spectra. The position of the alkyl substituent was confirmed by X-ray analysis. ORTEP diagrams of **5** and **6** in the asymmetric unit are presented in Figures 2 and 3, respectively.

3. Conclusions

Microwave activation of the Biltz synthesis of phenytoin improves both, yield and time reaction. Albeit yields under

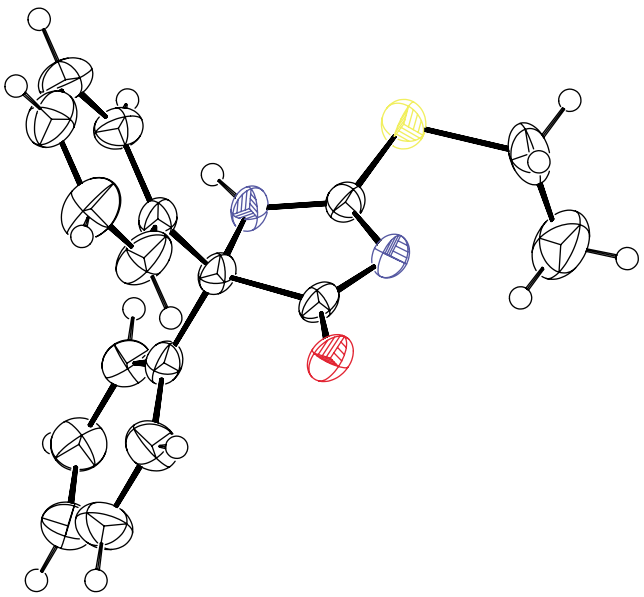


Figure 2. ORTEP diagram (50% probability) of *S*-ethyl-5,5′-diphenyl-2-thiohydantoin.

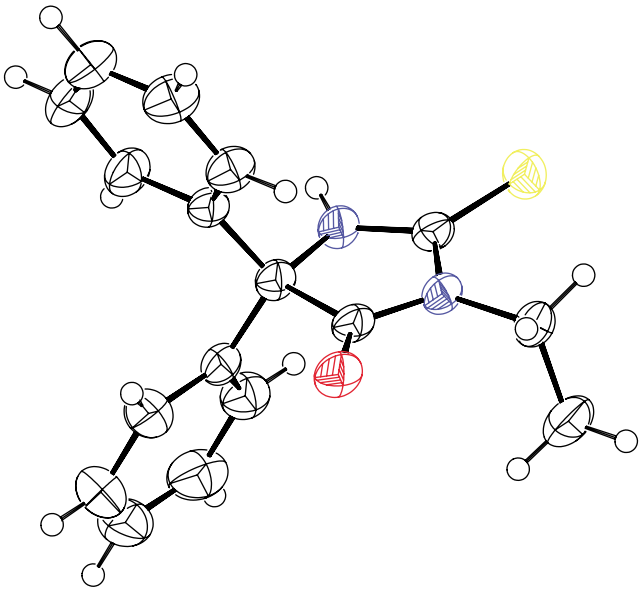


Figure 3. ORTEP diagram (50% probability) of 3-ethyl-5,5′-diphenyl-2-thioxo-imidazolidin-4-one.

microwave-assisted conditions were quite satisfactory (74%), a two-step synthesis was developed in order to reduce the formation of the glycolureide side product resulting in a further improvement of the yield (87.4%, total yield). This rapid method of synthesizing phenytoin can be very useful for the synthesis of radiolabelled phenytoin analogs with short half-lives.

Furthermore, using the corresponding alkylureas or alkylthioureas, the same microwave-assisted procedure gives rapid and efficient access to new N_3-alkyl-5,5′-diarylhydantoins or N_3-alkyl-5,5′-diaryl-2-thiohydantoins. This convenient procedure will allow a further increase of the diversity within the imidazolidinedione family.

4. Experimental

4.1. General procedures

All reagents were purchased from commercial sources (Sigma-Aldrich or Acros, Belgium) and were used without further purification. Solvents were of analytical grade. The microwave oven used was a commercial household microwave oven (Moulinex® FM1935G, frequency: 2450 MHz).

Melting points (mp) were determined in open capillaries using an Electrothermal 9100 apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Perkin–Elmer FT-IR 286 spectrometer, values are reported as ν in cm^{-1}. Nuclear magnetic resonance (^1H NMR, ^{13}C NMR) spectra were recorded on a Bruker AM-300 spectrometer at room temperature and analysed using the WIN NMR software package. Chemical shifts (δ) are reported relative to tetramethylsilane peak set at 0.00 ppm. In the case of multiplets the signals are reported as intervals. Signals were abbreviated as s, singlet; d, doublet; t, triplet; m, multiplet. Coupling constants were expressed in Hz. Mass spectra were recorded on a Finnigan MAT 44S, with an ionisation voltage of 70 eV.

Suitable crystals of compounds **5** and **6** obtained by recrystallization in ethanol were mounted with a quartz fibre on a goniometer head of a CAD4 Nonius diffractometer. After determination of the cell parameter using 25 well-centred reflections, complete diffraction data sets were collected. The structures were solved using direct methods and refined by full matrix least squares on F^2 using the program Shelxl97.[25] All non-hydrogen atoms were treated anisotropically while a riding model was applied for the hydrogens. Analytical correction for absorption was introduced.

4.1.1. Compound 5. Colourless plate (0.41×0.27×0.08 mm), monoclinic, $P2_1/c$, a=6.066(1) Å, b=18.587(1) Å, c=14.579(1) Å, α=90.0°, β=113.02(1)°, γ=90.0°, V=1512.9(3) Å^3, Z=4, μ=1.89 mm^{-1}, D_x=1.301 g cm^{-3}, λ (Cu Kα)=1.54178 Å, $F(000)$=624, T=290 K, 3264 unique reflections (R_{int}=0.0286), 195 refined parameters, R_1=0.0400 for 2977 $F_o>4\sigma(F_o)$, R_1=0.0503 for all data (3264) and wR_2=0.1098, GOF=S=1.054, $\Delta\rho_{min}$=−0.282 e/Å^3, $\Delta\rho_{max}$=0.199 e/Å^3.

4.1.2. Compound 6. Colourless plate (0.44×0.18×0.15 mm), monoclinic, $P2_1/c$, a=10.535(1) Å, b=12.360(1) Å, c=12.207(1) Å, α=90.0°, β=105.95(1)°, γ=90.0°, V=1528.3(2) Å^3, Z=4, μ=1.87 mm^{-1}, D_x=1.288 g cm^{-3}, λ (Cu Kα)=1.54178 Å, $F(000)$=624, T=290 K, 2985 unique reflections (R_{int}=0.0130), 196 refined parameters, R_1=0.0338 for 2687 $F_o>4\sigma(F_o)$, R_1=0.0382 for all data (2985) and wR_2=0.0965, GOF=S=1.032, $\Delta\rho_{min}$=−0.192 e/Å^3, $\Delta\rho_{max}$=0.270 e/Å^3.

4.1.3. 5,5′-Diphenyl-imidazolidine-2,4-dione (3a, X=O). *Classical method*. To a solution of 20.2 g of benzil (**1**, 96.2 mmol) and 12.69 g of urea (**2a**, 167 mmol) in 40 ml of DMSO 25 ml of 1.2 M aqueous KOH were added under stirring. The resulting mixture was refluxed for 2 h and poured into cold water. The precipitate was filtrated and the filtrate was acidified with glacial acetic acid. The resulting precipitate was collected, dried and recrystallized from ethanol. Yield=60%, mp 295–296°C. Spectral data similar to a commercial sample of the product (Acros Organics, 17173–0050).

Microwave activation. 25 ml of 1.2 M aqueous KOH were added to a mixture of 20.2 g of benzil (**1**, 96.2 mmol) and 10.03 g of urea (**2a**, 167 mmol) dissolved in 40 ml of DMSO. Following an initial 90 s 750 W pulse the mixture was stirred for 5 min. 30 s pulses were then applied at 6, 9, 12, 15, 18, 21, 24, and 30 min, the mixture was stirred between pulses. The mixture was then poured into 300 ml of cold water. The precipitate was filtrated and the filtrate was acidified with glacial acetic acid. The white precipitate was collected, dried and recrystallized from ethanol. Yield=74%. Mp 295–296°C. Spectral data similar to a commercial sample of the product (Acros Organics, 17173–0050).

4.1.4. 5,5′-Diphenyl-2-thioxo-imidazolidin-4-one (3b, X=S). The synthesis was performed as for **3a** (X=O), with microwave activation but using thiourea (**2b**).

Yield=92%. Mp 238–240°C. Spectral data similar to a commercial sample of the product (Sigma-Aldrich, D21,425-6).

4.1.5. Conversion of 5,5′-diphenyl-2-thioxo-imidazolidin-4-one (3b) into phenytoin (3a). To a solution of 2.68 g of 5,5′-diphenyl-2-thiohydantoin (10 mmol) in DMF 1 ml of glacial acetic acid and 2.5 ml of perhydrol 30% were added. The reaction mixture was stirred for 24 h at room temperature and poured onto ice. The precipitate was collected, dried, and recrystallized from ethanol. Yield=92%. Mp 294–296°C. Spectral data were comparable to (**3a**, X=O).

4.1.6. *S*-Ethyl-5,5′-diphenyl-2-thiohydantoin (5). The alkylation has been previously described for the 5-5′-diphenylhydantoin.[10] Briefly, 3 g of 5,5′-diphenyl-2-thiohydantoin (11.2 mmol) was dissolved in 10 ml of anhydrous DMF. K_2CO_3, 6.17 g (4.7 mmol) and iodo-ethane, 1.75 g (11.2 mmol) were added and the mixture stirred overnight. The mixture was poured into 150 ml of water. The resulting precipitate was collected, dried and recrystallized from ethanol. Yield=42%. Mp 182–184°C. ^{13}C NMR (300 Hz) δ 14.88 (CH_3), 23.87 (CH_2), 78.13 (C), 126.62 ($CH_{arom.}$), 127.46 ($CH_{arom.}$), 128.30 ($CH_{arom.}$), 140.53 ($C_{arom.}$), 159.55 (C_2), 181.94 (C=O). ^{1}H NMR (300 Hz) δ 1.35–1.39 (t, J=7.35 Hz, 3H), 3.18–3.25 (q, J=7.35 Hz, 2H), 7.31–7.37 (m, 10H), 11.52 (s, 1H). MS DEI: 296/100 $[M]^+$.

4.1.7. 3-Ethyl-5,5′-diphenyl-2-thioxo-imidazolidin-4-one (6). 25 ml of 1.2 M aqueous KOH were added to a mixture of 3 g of benzil (14.3 mmol) and 2.97 g of ethylthiourea (28.6 mmol) dissolved in 30 ml of DMSO. The resulting solution was subjected to a 90 s 750 W microwave pulse and stirred for 5 min. 30 s pulses were applied at 6, 9, 12, 15, 18, 21, 24, and 30 min, and the mixture was stirred between pulses. The mixture was poured into 300 ml of cold water. The resulting precipitate was collected, dried and recrystallized from ethanol. Yield=56%. Mp 186.8–187.4°C. IR (KBr, cm^{-1}) ν 3262 (NH), 1714 (C=O), 1495 (C=C), 1164 (C=S). ^{13}C NMR (300 Hz) δ 12.75 (CH_3), 35.71 (CH_2), 71.10 (C), 126.5524 ($CH_{arom.}$), 128.43 ($CH_{arom.}$), 128.75 ($CH_{arom.}$), 138.13 ($C_{arom.}$), 173.20 (C=S), 180.90 (C=O). ^{1}H NMR (300 Hz) δ 1.11–1.16 (m, 3H), 3.79–3.82 (m, 2H), 7.30–7.44 (m, 10H), 11.02 (s, 1H). MS DEI: 296/100 $[M]^+$.

4.1.8. 3-Cyclohexyl-5,5′-diphenyl-imidazolidine-2,4-dione (7). As described for **6** from 3 g of benzil (14.28 mmol) and 4.06 g of cyclohexylurea (28.56 mmol). Yield=58%. Mp 179–180°C. IR (KBr, cm^{-1}) ν 3233 (NH), 1770 (C=O), 1715 (C=O), 1493 (C=C). ^{13}C NMR (300 Hz) δ 24.88 (CH_2), 25.47 (CH_2), 29.15 (CH_2), 50.83 (CH), 68.36 (C), 126.72 ($CH_{arom.}$), 128.14 ($CH_{arom.}$), 128.60 ($CH_{arom.}$), 140.05 ($C_{arom.}$), 155.39 (C=O), 173.24 (C=O). ^{1}H NMR (300 Hz) δ 1.09–1.29 (m, 3H), 1.58–1.62 (m, 3H), 1.74–1.78 (m, 2H), 2.06–2.14 (m, 2H), 3.82–3.86 (m, 1H), 7.38–7.42 (m, 10H), 9.45 (s, 1H). MS DCI (H_2O): 335/100 $[M+H]^+$. Calcd for $C_{21}H_{20}Cl_2N_2O_2$: C, 62.54; H, 5.00; Cl, 17.58; N, 6.95; O, 7.93%. Found: C, 62.3; H, 4.95; Cl, 17.21; N, 6.86%.

4.1.9. 5,5′-Bis-(4-bromo-phenyl)-3-methyl-imidazolidine-2,4-dione (8). As described for **6** from 3 g of 4,4′-dibromobenzil (8.15 mmol) and 1.21 g of methylurea (16.3 mmol). Yield=45%. Mp 215–216°C. IR (KBr, cm^{-1}) ν 3218 (NH), 1769 (C=O), 1710 (C=O), 1480 (C=C). ^{13}C NMR (300 Hz) δ 24.59 (CH_3), 68.39 (C), 121.76 ($C_{arom.}$), 128.82 ($CH_{arom.}$), 131.53 ($CH_{arom.}$), 138.59 ($C_{arom.}$), 155.28 (C=O), 172.55 (C=O). ^{1}H NMR (300 Hz) δ 2.93 (m, 3H), 7.30 (d, J=8.82 Hz, 4H), 7.61 (d, J=8.82 Hz, 4H), 9.69 (s, 1H). MS DCI (H_2O): 425/100 $[M+H]^+$. Calcd for $C_{16}H_{12}Br_2N_2O_2$: C, 45.32; H, 2.85; Br, 37.68; N, 6.61; O, 7.55%. Found: C, 45.17; H, 2.78; N, 6.43%.

4.1.10. 5,5′-Bis-(4-bromo-phenyl)-3-ethyl-imidazolidine-2,4-dione (9). As described for **6** from 3 g of 4,4′-dibromobenzil (8.15 mmol) and 1.43 g of ethylurea (16.3 mmol). Yield=51%. Mp 215–216°C. IR (KBr, cm^{-1}) ν 3211 (NH), 1772 (C=O), 1712 (C=O), 1489 (C=C). ^{13}C NMR (300 Hz) δ 13.00 (CH_3), 33.13 (CH_2), 68.00 (C), 121.64 ($C_{arom.}$), 128.62 ($CH_{arom.}$), 131.47 ($CH_{arom.}$), 138.39 ($C_{arom.}$), 154.83 (C=O), 172.17 (C=O). ^{1}H NMR (300 Hz) δ 1.07–1.12 (m, 3H), 3.44–3.51 (m, 2H), 7.28 (d, J=8.82 Hz, 4H), 7.63 (d, J=8.82 Hz, 4H), 9.70 (s, 1H). MS DCI (H_2O): 439/100 $[M+H]^+$. Calcd for $C_{17}H_{14}Br_2N_2O_2$: C, 46.61; H, 3.22; Br, 36.48; N, 6.39; O, 7.3%. Found: C, 46.63; H, 3.24; N, 6.31%.

4.1.11. 5,5′-Bis-(4-bromo-phenyl)-3-butyl-imidazolidine-2,4-dione (10). As described for **6** from 3 g of 4,4′-dibromobenzil (8.15 mmol) and 1.89 g of butylurea (16.3 mmol). Yield=55%. Mp 151–152°C. IR (KBr, cm^{-1}) ν 3217 (N–H), 2954 (C–H), 1768 (C=O), 1713 (C=O), 1488 (C=C). ^{13}C NMR (300 Hz) δ 13.23 (CH_3), 19.05 (CH_2), 29.34 (CH_2), 37.75 (CH_2), 68.16 (C), 121.67 ($C_{arom.}$), 128.66 ($CH_{arom.}$), 131.50 ($CH_{arom.}$), 138.62 ($C_{arom.}$), 155.12 (C=O), 172.46 (C=O). ^{1}H NMR (300 Hz) δ 0.82–0.87 (m, 3H), 1.16–1.23 (m, 2H), 1.47–1.52 (m, 2H), 3.41–3.46 (m, 2H), 7.27 (d, J=8.82 Hz, 4H), 7.63 (d, J=8.82 Hz, 4H), 9.70 (s, 1H). MS DCI (H_2O): 467/100 $[M+H]^+$. Calcd for: $C_{19}H_{18}Br_2N_2O_2$: C, 48.95; H, 3.89; Br, 34.28; N, 6.01; O, 6.86%. Found: C, 48.65; H, 3.81; N, 5.93%.

4.1.12. 5,5′-Bis-(4-bromo-phenyl)-3-pentyl-imidazolidine-2,4-dione (11). As described for **6** from 3 g of 4,4′-dibromobenzil (8.15 mmol) and 2.12 g of pentylurea (16.3 mmol). Yield=54%. Mp 157–158°C. IR (KBr, cm^{-1}) ν 3215 (N–H), 2951 (C–H), 1766 (C=O), 1716 (C=O), 1490 (C=C). ^{13}C NMR (300 Hz) δ 13.36 (CH_3), 21.13 (CH_2), 26.62 (CH_2), 27.79 (CH_2), 37.75 (CH_2), 67.97 (C), 121.41 ($C_{arom.}$), 128.46 ($CH_{arom.}$), 131.24 ($CH_{arom.}$), 138.43 ($C_{arom.}$), 154.92 (C=O), 172.33 (C=O). ^{1}H NMR (300 Hz) δ 0.76–0.80 (m, 3H), 1.13–1.27 (m, 4H), 1.46–1.55 (m, 2H), 3.39–3.44 (t, J=7.35 Hz, 2H), 7.28 (d, J=8.82 Hz, 4H), 7.61 (d, J=8.82 Hz, 4H), 9.70 (s, 1H). MS DCI (H_2O): 481/100 $[M+H]^+$. Calcd for $C_{20}H_{20}Br_2N_2O_2$: C, 50.03; H, 4.20; Br, 33.28; N, 5.83; O, 6.66%. Found: C, 49.67; H, 4.11; N, 5.67%.

4.1.13. 5,5′-Bis-(4-chloro-phenyl)-imidazolidine-2,4-dione (12). As described for **3** with the microwave activation from 3 g of 4,4′-dichlorobenzil (10.79 mmol) and 1.64 g of urea (21.57 mmol). Yield=62%. Mp 318–320°C. IR (KBr, cm^{-1}) ν 3187 (NH),1772 (C=O), 1720

(C═O), 1490 (C═C). ^{13}C NMR (300 Hz) δ 69.23 (C), 128.43 ($CH_{arom.}$), 128.62 ($CH_{arom.}$), 132.02 ($C_{arom.}$), 138.46 ($C_{arom.}$), 155.73 (C═O), 174.17 (C═O). ^{1}H NMR (300 Hz) δ 7.36 (d, J=8.82 Hz, 4H), 7.49 (d, J=8.82 Hz, 4H), 9.40 (s, 1H), 11.25 (s, 1H). MS DCI (H_2O): 321/100 $[M+H]^+$.

4.1.14. 5,5′-Bis-(4-chloro-phenyl)-3-ethyl-imidazolidine-2,4-dione (13). As described for **6** from 3 g of 4,4′-dichlorobenzil (10.79 mmol) and 1.9 g of ethylurea (21.58 mmol). Yield=50%. Mp 160–161°C. IR (KBr, cm^{-1}) ν 3215 (NH), 1766 (C═O), 1710 (C═O), 1490 (C═C). ^{13}C NMR (300 Hz) δ 13.00 (CH_3), 33.19 (CH_2), 68.00 (C), 128.36 ($CH_{arom.}$), 128.62 ($CH_{arom.}$), 133.09 ($C_{arom.}$), 138.13 ($C_{arom.}$), 154.89 (C═O), 172.76 (C═O). ^{1}H NMR (300 Hz) δ 1.06–1.11 (t, J=7.35 Hz, 3H), 3.43–3.49 (q, J=7.35 Hz, 2H), 7.34 (d, J=8.82 Hz, 4H), 7.48 (d, J=8.82 Hz, 4H), 9.69 (s, 1H). MS DCI (H_2O): 349/100 $[M]^+$. Calcd for $C_{17}H_{14}Cl_2N_2O_2$: C, 58.47; H, 4.04; Cl, 20.30; N, 8.02; O, 9.16%. Found: C, 58.27; H, 4.11; Cl, 20.1; N, 7.96%.

4.1.15. 5,5′-Bis-(4-chloro-phenyl)-3-butyl-imidazolidine-2,4-dione (14). As described for **6** from 3 g of 4,4′-dichlorobenzil (10.79 mmol) and 2.57 g of butylurea (21.58 mmol). Yield=55%. Mp 145–146°C. IR (KBr, cm^{-1}) ν 3217 (NH), 1769 (C═O), 1713 (C═O), 1489 (C═O). ^{13}C NMR (300 Hz) δ 13.26 (CH_3), 19.22 (CH_2), 29.44 (CH_2), 37.85 (CH_2), 68.06 (C), 128.43 ($CH_{arom.}$), 128.69 ($CH_{arom.}$), 133.15 ($C_{arom.}$), 138.26 ($C_{arom.}$), 155.15 (C═O), 172.55 (C═O). ^{1}H NMR (300 Hz) δ 0.82–0.87 (t, J=7.35 Hz, 3H), 1.17–1.24 (q, J=7.35 Hz, 2H), 1.49–1.53 (m, 2H), 3.43–3.48 (t, J=7.35 Hz, 2H), 7.37 (d, J=8.82 Hz, 4H), 7.51 (d, J=8.82 Hz, 4H), 9.74 (s, 1H). MS DCI (H_2O): 377/100 $[M]^+$. Calcd for $C_{19}H_{18}Cl_2N_2O_2$: C, 60.49; H, 4.81; Cl, 18.79; N, 7.43; O, 8.48%. Found: C, 60.65; H, 4.89; Cl, 18.77; N, 7.3%.

4.1.16. 5,5′-Bis-(4-chloro-phenyl)-3-heptyl-imidazolidine-2,4-dione (15). As described for **6** from 3 g of 4,4′-dichlorobenzil (10.79 mmol) and 3.41 g of heptylurea (21.58 mmol). Yield=60%. Mp 150–151°C. IR (KBr, cm^{-1}) ν 3210 (NH), 1771 (C═O), 1708 (C═O), 1492 (C═C). ^{13}C NMR (300 Hz) δ 13.78 (CH_3), 21.80 (CH_2), 25.75 (CH_2), 27.17 (CH_2), 27.95 (CH_2), 30.99 (CH_2), 38.10 (CH_2), 68.1934 (C), 128.43 ($CH_{arom.}$), 128.69 ($CH_{arom.}$), 131.60 ($C_{arom.}$), 138.59 ($C_{arom.}$), 155.15 (C═O), 172.49 (C═O). ^{1}H NMR (300 Hz) δ 0.79–0.83 (m, 3H), 1.16 (m, 10H), 1.49–1.53 (m, 2H), 3.44 (t, J=7.35 Hz, 2H), 7.36 (d, J=8.82 Hz, 4H), 7.49 (d, J=8.82 Hz, 4H). MS DCI (H_2O): 419/100 $[M+H]^+$. Calcd for $C_{22}H_{24}Cl_2N_2O_2 \cdot 1/3H_2O$: C, 62.12; H, 5.85; Cl, 16.67; N, 6.59; O, 8.78%. Found: C, 62.42; H, 5.84; Cl, 16.72; N, 6.53%.

4.1.17. 5,5′-Bis-(4-chloro-phenyl)-3-cyclohexyl-imidazolidine-2,4-dione (16). As described for **6** from 3 g of 4,4′-dichlorobenzil (10.79 mmol) and 3.1 g of cyclohexylurea (21.58 mmol). Yield=57%. Mp 201–202°C. IR (KBr, cm^{-1}) ν 3202 (NH), 1769 (CO), 1710 (C═O), 1490 (C═C). ^{13}C NMR (300 Hz) δ 24.92 (CH_2), 25.76 (CH_2), 29.32 (CH_2), 52.09 (CH), 68.27 (C), 128.18 ($CH_{arom.}$), 129.02 ($CH_{arom.}$), 134.84 ($C_{arom.}$), 137.62 ($C_{arom.}$), 156.90 (C═O), 172.69 (C═O). ^{1}H NMR (300 Hz) δ 1.12–1.33 (m, 3H), 1.64–1.67 (m, 3H), 1.81–1.85 (m, 2H), 2.05–2.17 (m, 2H), 3.88–3.96 (m, 1H), 7.27 (d, J=8.82 Hz, 4H), 7.39 (d, J=8.82 Hz, 4H) 9.67 (s, 1H). MS DCI (H_2O): 403/100 $[M+H]^+$. Calcd for $C_{21}H_{20}Cl_2N_2O_2$: C, 62.54; H, 5; Cl, 17.58; N, 6.95; O, 7.93%. Found: C, 62.3; H, 4.95; Cl, 17.21; N, 6.86%.

4.2. Supplementary material for X-ray analysis

Crystallographic data (structures **5** and **6**) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 193953 and CCDC 193954. Copies of data can be obtained, free of charge, on application to CCDC (deposit@ccdc.cam.ac.uk).

Acknowledgements

One of us (G. M.) is very indebted to 'Fonds pour la formation à la Recherche dans l'Industrie et l'Agriculture (FRIA)', Belgium, for the award of a research fellowship. This work was partially funded by a FRSM grant from the Belgian National Fund for Scientific Research, a FSR grant from the Université catholique de Louvain.

References

1. Knabe, J.; Baldauf, J.; Ahlhem, A. *Pharmazie* **1997**, *52*, 912–919.
2. Sholl, S.; Koch, A.; Henning, D.; Kempter, G.; Kleinpeter, E. *Struct. Chem.* **1999**, *10*, 355–366.
3. Rodgers, T. R.; LaMontagne, M. P.; Markovac, A.; Ash, A. B. *J. Med. Chem.* **1977**, *20*, 591–594.
4. Bac, P.; Maurois, P.; Dupont, C.; Pages, N.; Stables, J. P.; Gressens, P.; Evrard, P. *J. Neurosci.* **1998**, *18*, 4363–4373.
5. Merrit, H. H.; Putnam, T. J. *Science* **1937**, *85*, 525.
6. Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *19*, 409.
7. Taylor, C. P. *Curr. Pharm. Des.* **1996**, *2*, 375–389.
8. Reagan, L. P.; McKittrick, C. R.; McEwen, B. S. *Neuroscience* **1999**, *91*, 211–219.
9. Park, K.-H.; Ehrler, J.; Spoerri, H.; Kurth, M.-J. *J. Comb. Chem.* **2000**, *3*, 171–176.
10. Kanyonyo, M.; Govaerts, S. G.; Hermans, E.; Poupaert, J. H.; Lambert, D. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2233–2236.
11. Ooms, F.; Wouters, J.; Oscari, O.; Happaerts, T.; Bouchard, G.; Carrupt, P. A.; Testa, B.; Lambert, D. M. *J. Med. Chem.* **2002**, *45*, 1748–1756.
12. For further information refer to: (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223.
13. Paul, S.; Gupta, M.; Gupta, R.; Loupy, A. *Synthesis* **2002**, *1*, 75–78.
14. Hayward, R. C. J. *J. Chem. Ed.* **1983**, *60*, 512.
15. Dunnavant, W. R.; James, F. L. *J. Am. Chem. Soc.* **1956**, *78*, 2740–2743.
16. Poupaert, J. H.; De Keyser, J. L.; Vandervorst, D.; Dumont, P. *Bull. Soc. Chim. Belg.* **1984**, *93*, 493–495.
17. Mergen, F.; Poupaert, J. H.; De Keyser, J. L.; Dumont, P. *Pharmazie* **1989**, *44*, 110–112.

18. Gong, Y.-D.; Kurth, M. J. *Tetrahedron Lett.* **1998**, *39*, 3379–3382.
19. Campbell, L. J.; Borges, L. F.; Heldrich, F. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2627–2630.
20. Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. *J. Org. Chem.* **1991**, *56*, 6968–6970.
21. Banik, B. K.; Manhas, M. S.; Newaz, S. N.; Bose, A. K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2363–2368.
22. Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Vegesna, S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, *30*, 471–474.
23. Butler, A. R.; Leitch, E. *J. Chem. Soc., Perkin Trans. 2* **1977**, *14*, 1972–1976.
24. Kehm, B. B.; Whitehead, C. W. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 515–516.
25. Sheldrick, G. *Shelxl97: Program for the refinement of molecular crystal structures*; University of Göttingen: Germany, 1997.