Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2014) 38: 629 – 637

doi:10.3906/kim-1310-30

Convenient synthesis of new polysubstituted isoindole-1,3-dione analogues

Ayşe TAN, Mustafa Zahrittin KAZANCIOĞLU, Derya AKTAŞ, Özlem GÜNDOĞDU, Ertan ŞAHİN†, Nurhan HORASAN KİSHALI*, Yunus KARA*

Department of Chemistry, Faculty of Sciences, Atatürk University, Erzurum, Turkey

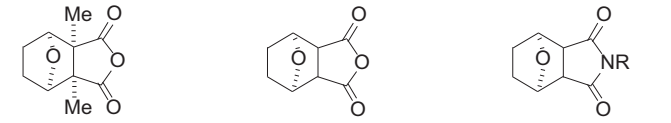
Received: 10.10.2013 • **Accepted:** 25.01.2014 • **Published Online:** 11.06.2014 • **Printed:** 10.07.2014

Abstract: Three new polysubstituted isoindole-1,3-diones were prepared from 2-ethyl-5-hydroxy-3a,4,5,7a-tetrahydro-isoindole-1,3-dione. The reaction of 2-ethyl-5-hydroxy-3a,4,5,7a-tetrahydro-isoindole-1,3-dione with m-CPBA gave the corresponding epoxide. The triacetate derivative was obtained via cis-hydroxylation using OsO_4, followed by acetylation. An aromatic derivative, a secondary reaction product, was also formed during the acetylation. Finally, a tricyclic derivative from 2-ethyl-5-hydroxy-3a,4,5,7a-tetrahydro-isoindole-1,3-dione was synthesized via dichloroketene addition under microwave irradiation. The exact structures of epoxide and tricyclic derivatives were determined by X-ray diffraction analysis.

Key words: Isoindole, norcantharimide, singlet oxygen, ketene, epoxidation

1. Introduction

Cantharidine (**1**) and its analogues norcantharidine (**2**) and norcantharimide (**3**) are important in that they show biological activity. Isoindole-1,3-diones, which are derivatives of cantharimides, have been a focus of interest as members of an important class of organic compounds with medicinal and biological activities (Figure 1).[1–7]



Cantharidine (1) Norcantharidine (2) Norcantharimide (3)

Figure 1. Structure of cantharidine (**1**), norcantharidine (**2**), and norcantharimide (**3**).

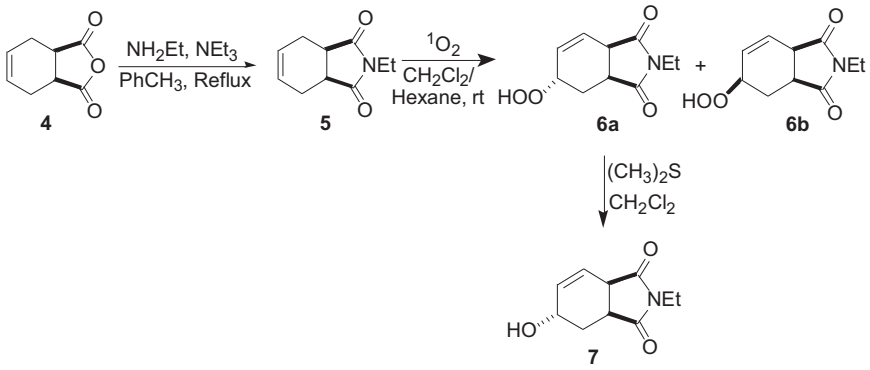
Derivatives of norcantharimide (**3**) are known to be potential anticancer agents. Both cantharimide and norcantharimide have been tested for their various effects.[2–11] N-Methyl-cantharimide is effective in tumor inhibition in animals and tests performed on xanthenes oxidase[12] also show these inhibitory effects. Cantharidin and its analogues have been found to be inhibitors of the serine/threonine protein phosphates 1 and 2A (PP1 and PP2A).[13]

McCluskey et al.[9] have synthesized various norcantharimides and investigated the cytotoxicity and anticancer activity of these derivatives. Lin et al.[10,11] have also reported the synthesis and anticancer activity of cantharimides against HepG2 and HL-60 cells.

*Correspondence: nhorasan@atauni.edu.tr, yukara@atauni.edu.tr
† To whom inquires concerning the X-ray structure should be directed.

Chan and Tang,[14] who also have investigated the synthesis and cytotoxicity of cantharimide derivatives, defined the potency of cantharimide since it has a less toxic effect on bone marrow cells suffering from nonmalignant hematological disorder.

Recently, we have developed a versatile synthetic approach that is applicable to the synthesis of new norcantharimide and amino phthalimide derivatives from 2-ethyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (**5**) (Scheme 1).[15–17]

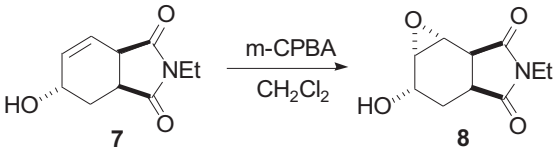


Scheme 1. General synthesis procedure of **7**.

This method is a practical application for the synthesis of norcantharimide derivatives in which the O-atom is easily incorporated into the molecule and its further reactions. To expand our recently reported method, we decided to develop a stereoselective route in forming new norcantharimide derivatives bearing acetoxy, hydroxy-epoxy, and cyclobutanone groups.

2. Results and discussion

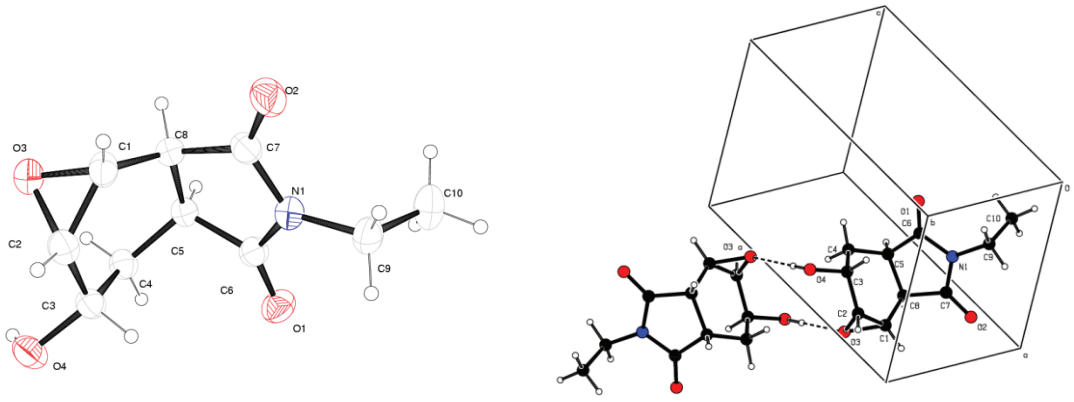
The starting material, **7**, was prepared according to the literature (Scheme 1).[15] For further chemical transformation, we decided to convert **7** to its corresponding epoxide. The allylic alcohol **7** was reacted with m-chloroperbenzoic acid. The ^{1}H NMR spectrum of the crude product indicated that the epoxide **8** was obtained as the sole product due to the syn effect of the allylic hydroxyl group (Scheme 2).[18] The exact structure of **8** was determined by X-ray diffraction analysis (Figure 2).



Scheme 2. The epoxidation of allylic alcohol **7**.

Compound **8** crystallizes in the triclinic space group P-1 with one complete molecule in the asymmetric unit (Figure 2a). The cyclohexane ring has a half-chair conformation. Maximum deviation from C(1)-C(2)-C(3)-C(5)-C(8) mean plane for the C(4) atom is 0.329 Å. The half-chair state is the transition state in the interconversion between the chair and twist-boat conformations. This is most probably due to the highly

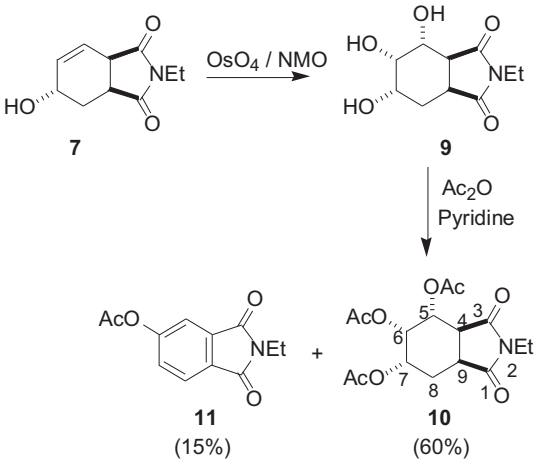
strained epoxide and its effective H-bonding with the neighboring OH group. Moreover, this effective H-bonding transforms the structure in the dimeric form (Figure 2b). As observed, epoxide and the OH groups are trans to the 1-ethyl-pyrrolidine-2,5-dione.



(a) (b)

Figure 2. a) ORTEP view of epoxide **8** showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level. b) H-bonding pattern (dashed lines) along the b-axis in the unit cell. O4 - H$\cdots$O3^{a} = 2.894(3) Å, < (O4 - H$\cdots$O3^{a}) = 180° [Symmetry code (a) 2 – x, 2 – y, 1 – z].

The allylic alcohol **7** is an ideal compound for the synthesis of triacetoxy norcantharimide derivatives. For this reason, the C=C bond in the alcohol **7** was cis-hydroxylated by OsO_4–NMO oxidation to give **9** (Scheme 3). After acetylation of the reaction mixture, triacetate **10** and acetoxy phthalimide **11** were isolated in a total yield of 75%.



Scheme 3. The synthesis of triacetate **10**.

The 2 faces of the C=C bond in **7** are not symmetric and the C=C bond can be attacked from both sides. We assume that OsO_4 approaches the double bond from the less congested side to form the alcohol **7**. It is likely that the nonbonded interactions between the substituents and OsO_4 are responsible for the exclusive anti-addition according to the imide ring. The formed triol **9** was converted to the corresponding acetate **10**. The configuration of the triacetate **10** was confirmed by ^{1}H NMR spectroscopy.

The acetoxyl resonances were assigned using the COSY spectrum and corresponding coupling constants between the acetoxyl protons were determined. The large coupling constant, J= 10 Hz, between the axial protons H_4 and H_5 confirmed the trans-configuration at the cyclohexane ring. Cis-configuration of the H_5/H_6 and H_6/H_7 adjacent protons was supported by the small coupling constants, $J_{5,6}$ and $J_{6,7}$ = 2.2 Hz.

The exact configuration of the triacetate **10** was confirmed by differential ^{1}H NMR-NOE measurements (Figure 3). The irradiation at the resonance signal of the H_6 at δ= 5.44 caused signal enhancements at the resonances of the adjacent protons H_5 and H_7 δ = 4.94 and 4.85, respectively. This experiment provided important information regarding the H_5, H_6, and H_7 protons, which show cis-stereochemistry.

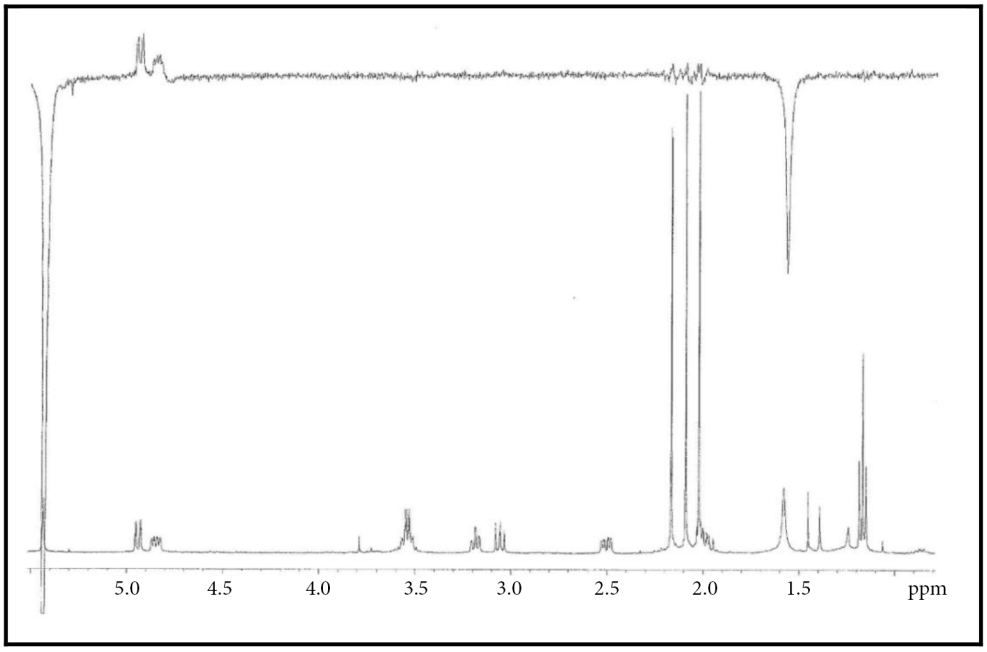
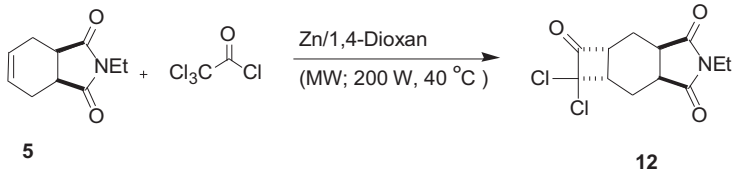


Figure 3. The ^{1}H NMR - NOE spectrums of triacetates.

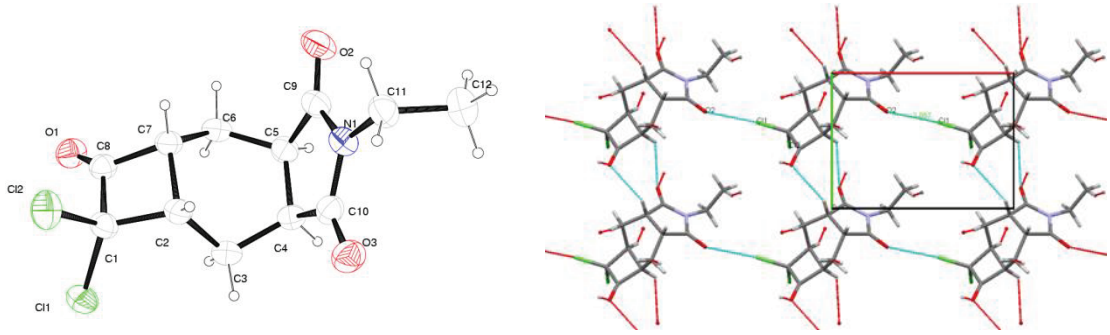
Formation of the secondary product **11** takes place via the triacetates **10** during acetylation. The structure of **11** was determined by ^{1}H and ^{13}C NMR spectroscopy. Signals of the aromatic H-atoms of **11** are highly characteristic. The ^{1}H NMR spectrum of **11** gave 2 doublets at 7.84 (J = 8.1 Hz) and 7.58 (J = 2.0 Hz) and 1 dd at 7.39 ppm (J = 8.1, 2.0 Hz). The ^{13}C NMR spectrum showed 3 C=O group signals, 6 aromatic carbons, and 3 aliphatic carbons. The double resonance spectrum and ^{13}C NMR spectrum are also fully consistent with this structure.

For the synthesis of another norcantharimide derivative, the imide **5** was reacted with dichloroketene under microwave irradiation. Compound **12** was obtained as the sole product (Scheme 4). ^{1}H and ^{13}C NMR spectroscopic data confirmed the addition of dichloroketene to the C=C bond.



Scheme 4. The dichloroketene [2+2] cycloaddition reaction of imide **5**.

We assume that the ketene approaches the C=C double bond from the less congested side to give the tricyclic compound **12**, similar to the hydroxylation reaction of alcohol **7**. The structure of **12** was assigned by ^{1}H and ^{13}C NMR spectra. The exact configuration of the addition product **12** was confirmed by X-ray analysis (Figure 4).

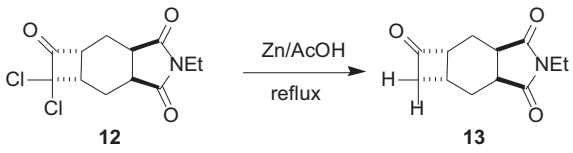


(a) (b)

Figure 4. a) ORTEP view of **12** showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level. b) The crystal packing of **12** as seen approximately along c-axis. Short contacts and Cl$\cdots$O halogen bonds are depicted as dashed lines.

The tricyclic compound **12** crystallizes in the monoclinic space group $P2_1/n$ with one complete molecule in the asymmetric unit (Figure 4a). The cyclohexane ring has the boat conformation (C(2)-C(4)-C(5)-C(7) torsion angle is –5.0°), which is less stable than the chair conformation. The orientation of the ketene is trans to the 1-ethyl-pyrrolidine-2,5-dione**.** The C(11)$\cdots$O(2) distance is 3.057(3) Å and well below the sum of van der Waals radii (3.3 Å). This kind of interaction is quite typical (Figure 4b).[19]

The subsequent reductive elimination of chlorine atoms in **12** was accomplished without complications using Zn in refluxing AcOH to give **13** in 70% yield (Scheme 5).



12 **13**

Scheme 5. The reductive elimination of **12**.

In summary, we have developed a route for the synthesis of 5 different isoindole-1,3-dione derivatives starting from readily available 3a,4,7,7a-tetrahydro-isobenzofuran-1,3-dione.[15] Studies of the biological activities and physical properties of phthalimide derivatives will be shared with the scientific community upon completion. This method has the potential to be widely used in organic synthesis as an easy way of constructing polysubstituted isoindole-1,3-dione derivatives.

3. Experimental

3.1. General

Column chromatography (CC): silica-gel 60 (70–230 mesh) and Alox (neutral Al_2O_3, type-III). Solvents were purified and dried by standard procedures before use. Mp: Büchi - 539 cap. Melting point apparatus;

uncorrected. ^{1}H and ^{13}C NMR spectra: Varian spectrometer, at 400 or 100 MHz; δ in ppm, J in Hz. Elemental analyses: Leco CHNS-932 instrument.

3.2. Synthesis of epoxide 8

To a stirred solution of **7**[15] (200 mg, 1.03 mmol) in CH_2Cl_2 (8 mL) was added m-CPBA 60% (356 mg, 1.24 mmol). The mixture was stirred overnight, the solid matter was removed by filtration, and the filtrate was washed with sat. $NaHCO_3$ solution (2 × 50 mL) and H_2O (50 mL), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave epoxide **8** (128 mg, 59%). Recrystallization of the epoxide **8** from CH_2Cl_2/n-hexane gave colorless crystal. Mp: 94–97 °C. ^{1}H NMR ($CDCl_3$): 3.94 (m, C$\underline{H}$OH), 3.57 (q, NC$\underline{H}_2$, J = 7.3), 3.56 (d, C$\underline{H}$OCH, J = 1.8), 3.34–3.32 (m, CHOC$\underline{H}$CH), 2.95 (ddd, $CH_2C\underline{H}$, J = 8.6, 6.2, 2.4), 2.33 (ddd, HOCHC$\underline{H}_a$H$_b$, J = 13.0, 2.2, 1.8), 2.02 (OH), 1.90 (ddd, HOCHCH$_a\underline{H}_b$, J = 6.2, 11.3, 13.0), 1.16 (t, $NCH_2C\underline{H}_3$, J = 7.3). ^{13}C NMR ($CDCl_3$): 178.2, 175.5, 64.9, 56.1, 54.8, 38.5, 38.6, 34.5, 25.5, 13.3.

3.3. Synthesis of 10 and 11

To a stirred solution of **7** (250 mg, 1.28 mmol) in acetone/H_2O (2 mL, 9:1) were added NMO (N-methylmorpholineoxide) (155.8 mg, 1.54 mmol) and OsO_4 (3.5 mg, 0.35 mL, 0.004 mmol) at 0 °C. The resulting mixture was stirred vigorously under N_2 at r.t. for 3 days. During the stirring the mixture became homogeneous. $NaHSO_3$ (0.01 g) and florisil (0.5 g) in H_2O (2 mL) were added, the slurry was stirred for 10 min, and the mixture was filtered through a pad of Celite (0.5 g) in a 50 mL sintered-glass funnel. The Celite cake was washed with acetone (3 × 10 mL). The filtrate was neutralized to pH 7 with H_2SO_4. The organic layer was removed under reduced pressure. The pH of the resulting aqueous solution was adjusted to 5 with H_2SO_4, and the diol **9** was separated from NMO by extraction with EtOAc (4 × 20 mL). The combined organic extracts were washed with 5 mL of 25% NaCl solution and 3 times with H_2O and dried (Na_2SO_4). Evaporation of the solvent gave 2-ethyl-4,5,6-trihydroxy-hexahydro-isoindole-1,3-dione (**9**), which was submitted to acetylation. For the acetylation, to a magnetically stirred solution of crude product **9** (290 mg, 1.27 mmol) in pyridine (1 mL) was added Ac_2O (521 mg, 5.1 mmol). The mixture was stirred at r.t. for 6 h and then cooled to 0 °C. After addition of diluted HCl (0.1 M, 50 mL), the H_2O phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with $NaHCO_3$ solution (2 × 25 mL) and H_2O (2 × 25 mL), and then dried (Na_2SO_4). Removal of the solvent under reduced pressure and ^{1}H NMR spectroscopic analysis of the residue revealed that the conversion was completed and 2 products, 5,6,7-diacetoxy-2-ethyl-1,3-dioxo-octahydro-isoindol (**10**) and 5-acetoxy-2-ethyl-1,3-dioxo-2,3-dihydro-1H-isoindol (**11**), were formed in a ratio of 6:1. Chromatography of the residue on silica gel (100 g) eluting with hexane/AcOEt (60:40) gave as the first fraction 5-acetoxy-2-ethyl-1,3-dioxo-2,3-dihydro-1H-isoindol (**11**) as a pale yellow liquid (43 mg, 14%). ^{1}H NMR ($CDCl_3$): 7.84 (d, 1H, J = 8.1), 7.58 (d, 1H, J = 2.0), 7.39 (dd, 1H, J = 2.0 , 8.1), 3.73 (q, 3H, J = 7.1), 2.35 (s, 3H), 1.26 (t, 3H, J = 7.0). ^{13}C NMR ($CDCl_3$): 168.8, 167.6, 167.4, 155.3, 134.3, 129.5, 127.2, 124.8, 117.3, 33.3, 21.3, 14.1.

As the second fraction, the major product triacetate 5,6,7-diacetoxy-2-ethyl-1,3-dioxo-octahydro-isoindol (**10**) was isolated. Recrystallization of the product from AcOEt/n-hexane gave **10** (273 mg, 60%) as a colorless solid. Mp: 181–183 °C. ^{1}H NMR ($CDCl_3$): 5.44 (t, H$_6$, J = 2.2), 4.95 (dd, H$_5$, J = 9.9, 2.2), 4.85 (ddd, H$_7$, J = 12.1, 5.5, 2.2), 3.54 (q, $NC\underline{H}_2CH_3$, J = 7.3), 3.18 (td, H$_4$, J = 8.1, 2.0), 3.06 (dd, H$_9$, J = 9.9, 8.1),

2.50 (ddd, H_{8a}, J = 13.6, 5.5, 2.0), 2.17 (s, $COC\underline{H}_3$), 2.09 (s, $COC\underline{H}_3$), 2.02 (s, $COC\underline{H}_3$), 1.99 (m, H_{8b}), 1.17 (t, $NCH_2C\underline{H}_3$, J = 7.3). ^{13}C NMR ($CDCl_3$): 176.3, 175.8, 169.9, 169.6, 169.5, 68.9, 68.6, 67.1, 41.6, 38.2, 34, 20.9, 20.8, 20.7, 20.6, 12.9. Anal. calc. for $C_{16}H_{21}NO_8$ (355,13): C 54.08, H 5.96, N 3.94; found: C 53.72, H 5.88, N 3.99.

3.4. Synthesis of 6,6-dichloro-2-ethyl-hexahydro-cyclobuta[f]isoindole-1,3,5-trione (12)

To a 50-mL flame-dried round-bottom flask were added 980 mg (5.5 mmol) of **5**, 10 mL of [1,4]-dioxane, 1.23 mL (1.99 mg, 11 mmol) of trichloroacetyl chloride, and 750 mg (11 mmol) of Zn powder. The resulting mixture was placed into a microwave reactor (200 W, 40 °C) (CEM, Matthews, NC, USA). The reaction was completed in 20 min and then Et_2O was added to the flask. The solids were removed by simple filtration. The filtrate was extracted first with H_2O (2 × 100 mL) and then with saturated $NaHCO_3$ (2 × 100 mL). The organic solution was dried (Na_2SO_4) and the solvent was evaporated. Crystallization of the product from CH_2Cl_2/n-hexane gave 6,6-dikloro-2-ethylhexahydro-1H-cyclobuta[f]isoindole-1,3,5-trione **12** (0,6 mg, 38%) as white crystals. Mp: 116–117 °C. ^{1}H NMR ($CDCl_3$): 3.78 (dd, H_4, J = 8.1, 10.3), 3.57 (q, $NC\underline{H}_2$, J = 7.3), 3.12 (ddd, H_{3a}, J = 9.9, 5.5, 4.4, A part of AB system), 3.01 (ddd, H_{7a}, J = 13.9, 4.4, 3.7, B part of AB system), 2.76 (dd, H_{6a}, J = 11.0, 5.9), 2.37 (m, $H_{4,7}$, A part of 2 AB systems), 1.99 (ddd, H_4, J = 16.2, 10.3, 5.9, B part of AB system), 1.86 (ddd, H_7, J = 17.2, 11.3, 5.9, B part of AB system), 1.24 (t, NCH_2C_{H3}, J = 7.3). ^{13}C NMR ($CDCl_3$): 194.6, 178.4, 178.3, 88.2, 51.1, 41.6, 36.8, 36.5, 34.3, 22.5, 19.0, 13.2. Anal. calc. for $C_{12}H_{13}Cl_2NO_3$ (289.03 g/mol): C 49.68, H 4.52, N 4.83; found: C 49.61, H 4.35, N 4.95.

3.5. Synthesis of 2-ethylhexahydro-cyclobuta[f]isoindole-1,3,5-trione (13)

A solution of dichloroketone **12** (600 mg, 2.07 mmol) in AcOH (25 mL) was added dropwise to a suspension of Zn vigorously stirred (280 mg, 4.14 mmol) in glacial AcOH (50 mL) at r.t. After the addition was complete, the mixture was maintained to reflux for 24 h. Then it was cooled to r.t. and stirred for an additional 4 h. To dissolve the formed Zn salts water was added. The resulting mixture was treated with EtOAc, and the Zn residue was filtered. Consecutively, the organic layer was washed with $NaHCO_3$ solution, 3 times with H_2O and a sat. $NaHCO_3$ solution to remove AcOH, and dried over $MgSO_4$. The solvent was removed under vacuum. Crystallization of the product from CH_2Cl_2/n-hexane gave **13** (0.38 g, 1.72 mmol, 83%) as white crystals. Mp: 68–69 °C. ^{1}H NMR ($CDCl_3$): 3.55 (q, $NC\underline{H}_2$, J = 7.3), 3.33 (m, H_6), 3.04 (dt, H_{3a}, J = 4.8, 9.5, A part of AB system), 2.29 (dt, H_{3b}, J = 5.2, 9.5, B part of AB system), 2.77 (m, H_4), 2.32 (m, H_{4a}), 2.17 (m, H_{6a}), 1.92 (ddd, H_7, J = 5.9, 10.3, 15.7, A part of AB system), 1.68 (ddd, H_7, J = 5.5, 10.3, 15.7, B part of AB system), 1.15 (t, $NCH_2C\underline{H}_3$, J = 7.3). ^{13}C NMR ($CDCl_3$): 209.5, 179.5, 179.2, 54.6, 52.5, 38.0, 36.6, 34.1, 25.6, 19.6, 19.0, 13.3. Anal. calc. for $C_{12}H_{15}NO_3$ (221.11 g/mol): C 65.14, H 6.83, N 6.33; Found: C 64.81, H 6.75, N 6.25.

3.6. Crystallography

For the crystal structure determination, a single crystal of compounds **8** and **12** was used for data collection on a 4-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a 2-dimensional area IP detector). Graphite-monochromated Mo–K_α radiation (λ = 0.71073 Å) and oscillation scans technique with $\Delta w = 5^\circ$ for 1 image were used for data collection. The lattice parameters were determined by the least-squares method on the basis

of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects, and cell refinement were performed using CrystalClear (Rigaku/MSC Inc., 2005) software.[20] The structures were solved by direct methods using SHELXS-97[21] and refined by a full-matrix least-squares procedure also using SHELXL-97.[21] H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. Crystal data for **8**: $C_{10}H_{13}NO_4$, crystal system, space group: monoclinic, $P2_1/n$; (no: 14); unit cell dimensions: a = 6.7632(2), b = 7.0863(3), c = 10.3539(4) Å, α = 97.172(5), β = 95.492(4), γ = 94.766(5) Å; volume: 487.81(3) Å^3; Z = 2; calculated density: 1.438 g/cm^3; absorption coefficient: 0.112 mm^{-1} ; F(000): 224; θ-range for data collection 2.9–26.4°; refinement method: full matrix least-square on F^2; data/parameters: 1992/139; goodness-of-fit on F^2: 1.051; final R-indices [$I > 2\sigma(I)$]: R_1 = 0.066, wR_2 = 0.182; largest diff. peak and hole: 0.303 and –0.211 e Å^{-3}. Crystal data for **12**: $C_{12}H_{13}NO_3Cl_2$, crystal system, space group: monoclinic, $P2_1/n$; (no: 14); unit cell dimensions: a = 9.7024(3), b = 7.1974(3), c =18.6969(8) Å, α = 90, β = 91.823(4), γ = 90 Å; volume: 1304.98(9) Å^3; Z = 4; calculated density: 1.477 g/cm^3; absorption coefficient: 0.496 mm^{-1}; F(000): 600; θ-range for data collection 2.2–26.5°; refinement method: full matrix least-square on F^2; data/parameters: 2670/164; goodness-of-fit on F^2: 0.982; final R-indices [$I > 2\sigma$ (I)]: R_1 = 0.0703, wR_2 = 0.110; largest diff. peak and hole: 0.383 and –0.477 e Å^{-3}.

CCDC 938983 (**8**) and CCDC 939530 (**12**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx? (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgments

The authors would like to thank Atatürk University for its financial support (Grant No: 2010/283). We would also like to thank Bilal Altundas for the helpful discussion.

References

1. Southcott, C.V. *Med. J. Aust.* **1989**, *151*, 654–659.
2. Fahmy, A. F. *Arkivoc.* **2006**, *7*, 395–415.
3. Hargreaves, M. K.; Pritchard, J. G.; Dave, H. R. *Chem. Rev.* **1970**, *70*, 439–469.
4. Kato, Y.; Ebiik, H.; Achiwa, K.; Kurihara, T.; Kobayashi, F. *Chem. Pharm. Bull.* **1990**, *38*, 2060–2062.
5. Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M.; Urzus, A.; Fajardo, V. *Tetrahedron* **1984**, *40*, 3957–3962.
6. Priestap, H. A. *Phytochemistry* **1985**, *24*, 849–852.
7. Shaikhiev, I. G.; Fridland, S. V.; Mukhutdinova, G. M. *Russ. J. Gen. Chem.* **1999**, *69*, 557–559.
8. Tsauer, W.; Lin, J. G.; Lin, P. Y.; Hsu, F. L.; Chiang, H. C. *Anticancer Res.* **1997**, *17*, 2095–2098.
9. Hill, T. A.; Stewart, S. G.; Ackland, S. P.; Gilbert, J.; Sauer, B.; Sakoff, J. A.; McCluskey, A. *Bioorg. Med. Chem.* **2007**, *15*, 6126–6134.
10. Lin, L. H.; Huang, H. S.; Lin, C. C.; Lee, L. W.; Lin, P-Y. *Chem. Pharm. Bull.* **2004**, *52*, 855–857.
11. Lin, P. Y.; Shi, S. J.; Shu, H. L.; Chen, H. F.; Lin, C. C.; Liu, P. C.; Wang, L. F. *Bioorg. Chem.* **2000**, *28*, 266–272.
12. Sheppeck, J. E.; Gauss, C. M.; Chamberlin, A. R. *Bioorg. Med. Chem.* **1997**, *5*, 1739–1750.

13. McCluskey, A.; Walkom, C.; Bowyer, M. C.; Ackland, S. P.; Gardinera, E.; Sakoff, J. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2941–2946.

14. Hon, S.; Kok, L.; Chui, C. H.; Lam, W. S.; Chen, J.; Lau, F. Y.; Wong, R. S. M.; Cheng, G. Y. M.; Lai, P. B. S.; Leung, T. W. T.; et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1155–1159.

15. Tan, A.; Koc, B.; Şahin, E.; Kishali, N. H.; Kara Y. *Synthesis* **2011**, *7*, 1079–1084.

16. Cope, A. C.; Herrick, E. C. *Org. Synth. Coll.* **1963**, *4*, 890–892.

17. Asaki, T.; Aoki, T.; Hamamoto, T.; Sugiyama, Y.; Ohmachi, S.; Kuwabara, K.; Murakami, K.; Todo, M. *Bioorg. Med. Chem.* **2008**, *16*, 981–994.

18. Kishali, N. H.; Dogan, D.; Sahin, E.; Gunel, A.; Kara, Y.; Balci, M. *Tetrahedron* **2011**, *67*, 1193–1200.

19. Kubicki, M. *J. Mol. Struct.* **2004**, *698*, 67–73.

20. Rigaku/MSC, Inc.: 9009 New Trails Drive, The Woodlands, TX 77381.

21. Sheldrick, G. M. SHELXS97 and SHELXL97; University of Göttingen: Germany, 1997.