Tetrahedron Letters 54 (2013) 6804–6806

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Formation of tryptanthrin compounds upon Oxone-induced dimerization of indole-3-carbaldehydes

Amber C. Nelson, Emily S. Kalinowski, Taylor L. Jacobson, Peter Grundt *

Department of Chemistry & Biochemistry, University of Minnesota Duluth, 1039 University Drive, Duluth, MN 55812, United States

ARTICLE INFO

Article history:
Received 18 November 2012
Revised 27 September 2013
Accepted 28 September 2013
Available online 3 October 2013

Keywords:
Natural product synthesis
Tryptanthrin
Oxidation

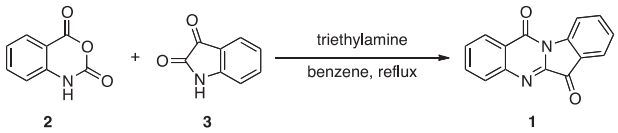
ABSTRACT

Tryptanthrin is a natural product with numerous important pharmacological properties. Tryptanthrin and its analogs are commonly prepared by condensation of isatoic anhydride and isatin. In this Letter we investigate the formation of tryptanthrin derivatives upon Oxone-induced oxidative dimerization of indole-3-carbaldehydes.

Introduction

Tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione, **1**, Scheme 1) is a natural product, which shows significant biological activity. The biological activity demonstrated by tryptanthrin and its derivatives pertains to antibacterial,[1] antiparasitic,[2] and antineoplastic[3] properties. Our interest in these compounds stems from their ability to inhibit the lifecycle of the parasite *Toxoplasma gondii*.

Tryptanthrin compounds are highly functionalized molecules. Fortunately, the synthesis of this class of compounds can be easily achieved from readily available starting materials.[4] The most common approach for the synthesis of these compounds involves the condensation of isatoic anhydride (**2**) and isatin (**3**) to give tryptanthrin in moderate to high yields. The driving force for this reaction is the development of carbon dioxide and water. If weak bases are used, such as triethylamine or morpholine, then heat is required to induce the formation of tryptanthrin. However, in the presence of strong bases such as sodium hydride or water scavengers, tryptanthrin forms even at room temperature. Interestingly, in the presence of β-cyclodextrin as the catalyst tryptanthrin compounds can form in water without adding base at room temperature.[5]



2 3 1

Scheme 1. Laboratory synthesis of the natural product tryptanthrin (**1**).

There are numerous alternative procedures and methods to synthesize tryptanthrin compounds. Several groups have investigated the dimerization of isatin (**3**) as an approach to obtain these compounds. This procedure has been achieved electrochemically,[6] by radiation with laser light[7] and in the presence of an oxidizing agent; such as potassium permanganate.[8] Alternatively, a very elegant method was developed by Moskovkina et al. These researchers induced the dimerization of isatin (**3**) by phosphoryl chloride.[9]

The synthesis of tryptanthrin and its derivatives has also been achieved by dimerization of other heterocycles. During the preparation of this manuscript Wang et al. disclosed copper-catalyzed aerobic oxidation of indole as the method to access this class of compounds.[10]

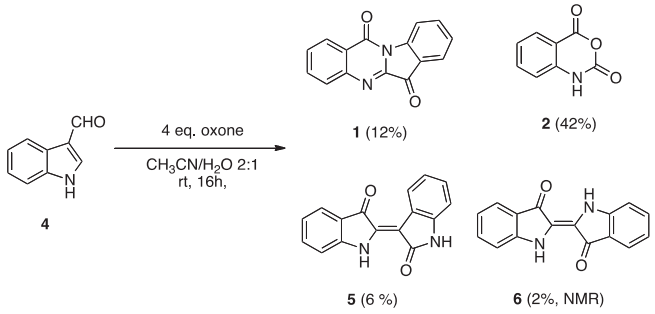
In this Letter we consider the formation of tryptanthrin compounds as a result of the Oxone-induced oxidation of indole-3-carbaldehydes. Oxone, a potassium triple salt containing potassium peroxymonosulfate, is a versatile oxidant.[11] Compared to other oxidation reagents, Oxone is particularly attractive in part due to its stability, nontoxic nature, and non-polluting by-products. Oxone induces numerous oxidation reactions. However, there are only limited examples that show the effect of Oxone on indole compounds.[12,13]

Results and discussion

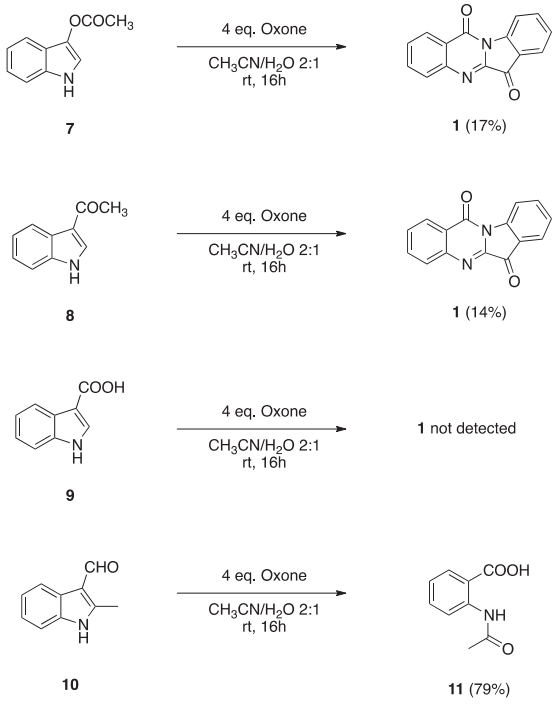
When we treated indole-3-carbaldehyde (**4**, Scheme 2) in a 2:1 mixture of acetonitrile/water at room temperature with an excess of Oxone we were able to isolate the following products: tryptanthrin (**1**), isatoic anhydride (**2**), and indirubin (**5**). From ^{1}H

* Corresponding author. Tel.: +1 218 726 6939; fax: +1 218 726 7394.
E-mail address: pgrundt@d.umn.edu (P. Grundt).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.09.124



Scheme 2. Observed products from the Oxone induced oxidation of indole-3-carbaldehyde (**4**) at room temperature.



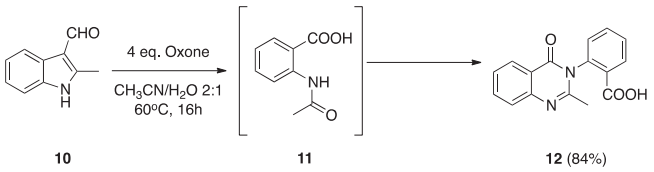
Scheme 3. Oxone induced oxidations of the indole compounds **7**–**10** at room temperature.

NMR of the crude reaction mixture were able to identify indigo (**6**). In addition, the GC/MS spectrum of the crude mixture indicated the presence of a trace amount of isatin (**3**).

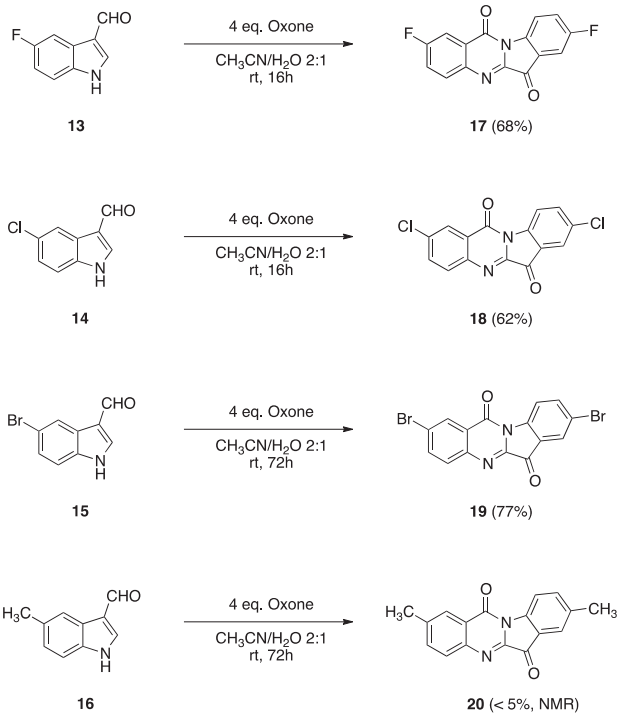
The formation of tryptanthrin (**1**), indirubin (**5**), and indigo (**6**) during the Oxone-induced oxidation of **4** is the result of a dimerization of the starting material. In addition to an oxidation of the 2,3-double bond in the indole moiety of **4**, all of these products, as well as isatoic anhydride (**2**) require a decarboxylation of the aldehyde group. The outcome of the Oxone induced oxidation of **4** appeared to be strongly dependent on the reaction conditions. We found that just a small increase of the temperature from 25 to 40 °C was sufficient to inhibit the formation of **1**. The parent indole compound appeared not to form **1** under any tested reaction conditions and led to isatoic anhydride.[13]

However, when we treated indoxyl-3-acetate (**7**, Scheme 3) and 3-acetyl indole (**8**) with Oxone, tryptanthrin (**1**) was isolated with 17% and 14% yields, respectively. In each case the ^{1}H NMR of the crude product mixture appeared to be very similar to the one recorded for the oxidation of **4**.

It is well known that Oxone induces oxidations of aldehydes to carboxylic acids via a Baeyer Villiger type mechanism.[14] Assuming



Scheme 4. Oxidation of aldehyde **10** at 60 °C results in quinazoline **12**.



Scheme 5. Oxidation of the aldehydes **13**–**16**.

that the oxidation of the aldehyde group in **4** is faster than the oxidation of the 2,3-double bond in the indole moiety, the carboxylic acid **9** can be envisioned to be an intermediate in this reaction. However, we found that the oxidation of **9** (Scheme 3) led to a complex mixture of different, and at this point unidentified, products. Additionally, we were unable to identify **1** in the crude reaction mixture.

A methyl group in 2-position of the indole moiety blocked the formation of **1**. For the oxidation of aldehyde **10** at room temperature the endpoint was *N*-acetyl anthranilic acid (**11**) that was isolated with 79% yield (Scheme 3). 2-Methyl indole reacted similarly and gave the same compound. No other products were detected under these reaction conditions. Once heat was applied (60 °C, overnight) **11** readily dimerized to form the quinazoline compound **12** (Scheme 4).

We tested the outcome of the oxidation of indole 3-carbaldehydes with substituents in 5-position. We were delighted to find that when we treated the indole-3-carbaldehydes **13**–**15** (Scheme 5) with Oxone at room temperature we were able to isolate the tryptanthrin compounds **17**–**19** in moderate to good yields. Treatment of the 5-methyl derivative **16** with Oxone resulted in a complex mixture with only a small amount (<5%) of 2,8-dimethyl tryptanthrin (**20**) being observed in the ^{1}H NMR spectrum.

In general the formation of tryptanthrin compounds by Oxone induced dimerization appeared to be limited to indole compounds with a halogen in the 5-position of the aryl moiety. While aldehyde **15** when treated with Oxone in a mixture of 2:1 CH_3CN/H_2O

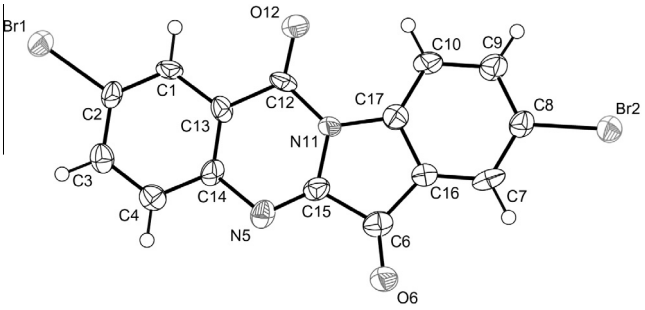


Figure 1. X-ray structure of **19**.

readily dimerized to form (**19**), its isomers such as 4-bromo-, 6-bromo-, or 7-bromo-indole-3-carbaldehyde did not form the corresponding tryptanthrin compounds. At this point the reasons for this observation are unclear. However, in orientating experiments we failed to successfully prepare these unknown analogs by condensation of the appropriate isatoic anhydrides and isatins in refluxing benzene.

All compounds were identified by comparison with authentic samples and characterized by NMR,[15] mass, and microanalysis. The identity of the tryptanthrin compound **19** was further confirmed by X-ray diffraction (Fig. 1). Compound **19** crystallized in a centrosymmetric P 21/n space group with 4 independent molecules in the asymmetric unit. The conjugated four-ring system is essentially planar in each molecule [maximum deviation = 0.037 (10) Å].

Conclusions

We were able to show that the tryptanthrin compounds can be synthesized by Oxone induced oxidation of indole-3-carbaldehyde and its 5-halogen substituted analogs. Further studies are underway to determine the mechanism of this reaction.

Acknowledgments

This study was supported by funds from the University of Minnesota Undergraduate Research Program (UROP) and the NSF (Grant CHE-0922366 for X-ray diffractometer).

References and notes

1. (a) Honda, G.; Tabata, M.; Tsuda, M. *Planta Med.* **1979**, *37*, 172; (b) Mitscher, L. A.; Baker, W. R. *Pure Appl. Chem.* **1998**, *70*, 365; (c) Kataoka, M.; Hirata, K.; Kunikata, T.; Ushio, S.; Iwaki, K.; Ohashi, K.; Ikeda, M.; Kurimoto, M. *J. Gastroenterol.* **2001**, *36*, 5; (d) Bandekar, P. P.; Roopnarine, K. A.; Parekh, V. J.; Mitchell, T. R.; Novak, M. J.; Sinden, R. R. *J. Med. Chem.* **2010**, *53*, 3558.
2. (a) Bhattacharjee, A. K.; Skanchy, D. J.; Jennings, B.; Hudson, T. H.; Brendle, J. J.; Werbovetz, K. A. *Bioorg. Med. Chem.* **2002**, *10*, 1979; (b) Scovill, J.; Blank, E.; Konnick, M.; Nenortas, E.; Shapiro, T. *Antimicrob. Agents Chemother.* **2002**, *46*, 882; (c) Bhattacharjee, A. K.; Hartell, M. G.; Nichols, D. A.; Hicks, R. P.; Stanton, B.; Van Hamont, J. E.; Milhous, W. K. *Eur. J. Med. Chem.* **2004**, *39*, 59; (d) Krivogorsky, B.; Grundt, P.; Yolken, R.; Jones-Brando, L. *Antimicrob. Agents Chemother.* **2008**, *52*, 4466; (e) Krivogorsky, B.; Nelson, A. C.; Douglas, K. A.; Grundt, P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1032.
3. (a) Motoki, T.; Takami, Y.; Yagi, Y.; Tai, A.; Yamamoto, I.; Gohda, E. *Biol. Pharm. Bull.* **2005**, *28*, 260; (b) Yu, S.-T.; Chen, T.-M.; Tseng, S.-Y.; Chen, Y.-H. *Biochem. Biophys. Res. Commun.* **2007**, *358*, 79; (c) Sharma, V. M.; Prasanna, P.; Adi Seshu, K. V.; Renuka, B.; Laxman Rao, C. V.; Sunil Kumar, G.; Narasimhulu, C. P.; Aravind Babu, P.; Puranik, R. C.; Subramanyam, D.; Venkateswarlu, A.; Rajagopal, S.; Kumar, K. B. S.; Rao, C. S.; Mamidi, N. V. S. R.; Deevi, D. S.; Ajaykumar, R.; Rajagopalan, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2303.
4. Tucker, A. M.; Grundt, P. *ARKIVOC* **2012**, *1*, 546–569.
5. Kumar, A.; Tripathi, V. D.; Kumar, P. *Green Chem.* **2011**, *13*, 51.
6. (a) Becker, J. Y.; Shakkour, E. *Tetrahedron* **1994**, *50*, 12773; (b) Batanero, B.; Barba, F. *Tetrahedron Lett.* **2006**, *47*, 8201.
7. Karpf, H.; Junek, H. *Tetrahedron Lett.* **1978**, *19*, 3007.
8. Zou, J.; Huang, L. *Acta Pharmacol. Sin.* **1985**, *20*, 45.
9. (a) Moskovkina, T. V. *Russ. J. Org. Chem.* **1997**, *33*, 125; (b) Moskovkina, T.; Kalinovskii, A.; Makhan'kov, V. *Russ. J. Org. Chem.* **2012**, *48*, 123.
10. Wang, C.; Zhang, L.; Ren, A.; Lu, P.; Wang, Y. *Org. Lett.* **2013**, *15*, 2982.
11. (a) Hussain, H.; Green, I. R.; Ahmed, I. *Chem. Rev.* **2013**, *113*, 3329; (b) Marcotullio, M. C.; Epifano, F.; Curini, M. *Trends Org. Chem.* **2003**, *10*, 21.
12. (a) Gao, X.-A.; Yan, R.-L.; Wang, X.-X.; Yan, H.; Li, J.; Guo, H.; Huang, G.-S. *J. Org. Chem.* **2012**, *77*, 7700; (b) Meenakshisundaram, S.; Sarathi, N. *Int. J. Chem. Kinet.* **2006**, *39*, 46; (c) Kavery, M.; Govindasamy, C.; Johnson, S. *J. Korean Chem. Soc.* **2013**, *57*, 210; (d) Umemoto, H.; Umemoto, M.; Ohta, C.; Dohshita, M.; Tanaka, H.; Hattori, S.; Hamamoto, H.; Miki, Y. *Heterocycles* **2009**, *78*, 2845; (e) Chandramohan, G.; Kalyanasundharam, S.; Renganathan, R. *Int. J. Chem. Kinet.* **2002**, *34*, 569; (f) Wu, G.; Liu, Q.; Shen, Y.; Wu, W.; Wu, L. *Tetrahedron Lett.* **2005**, *46*, 5831; (g) Wu, G.; Wu, J.; Wu, J.; Wu, L. *Synth. Commun.* **2008**, *38*, 1036; (h) Kumar, C. V.; Shivananda, K. N.; Raju, C. N.; Jagadeesh, R. V. *Synth. Commun.* **2010**, *40*, 3480; (i) Karthikeyan, P.; Jagadeesh, R. V.; Sree, S. Y.; Puttaswamy Nithya, P.; Senthil, K. S.; Bhagat, P. R. *Appl. Organomet. Chem.* **2011**, *25*, 34; (j) Dupeyre, G.; Lemoine, P.; Ainseba, N.; Michel, S.; Cachet, X. *Org. Biomol. Chem.* **2011**, *9*, 7780; (k) d'Ischia, M.; Prota, G. *Gazz. Chim. Ital.* **1986**, *116*, 407; (l) Lian, X.-L.; Lei, H.; Quan, X.-J.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Commun.* **2013**, *49*, 8196.
13. Nelson, A. C.; Kalinowski, E. S.; Czerniecki, N. J.; Jacobson, T. L.; Grundt, P. *Org. Biomol. Chem.* **2013**, *11*, 7455.
14. Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.
15. *Selected NMR data (if not indicated otherwise DMSO-d_6):* Compound **1**: ^{1}H NMR: δ 8.46 (d, *J* 7.8, 1H), 8.30 (d, *J* 7.8, 1H), 7.92–7.94 (m, 2H), 7.83–7.88 (m, 2H), 7.73 (m, 1H), 7.47 (t, *J* 7.8, 1H). ^{13}C NMR: δ 182.3, 157.6, 146.3, 145.9, 144.9, 137.6, 135.0, 129.8, 129.7, 126.8, 126.8, 124.6, 123.2, 122.1, 116.9. Compound **17**: ^{1}H NMR: δ 8.48 (dd, *J* 8.8, 4.1, 1H), 8.07–8.01 (m, 2H), 7.85 (td, *J* 8.6, 3.0, 1H), 7.80 (dd, *J* 7.0, 2.6, 1H), 7.74 (td, *J* 8.9, 2.6, 1H). ^{13}C NMR: δ 180.1 (J_{CF} 2), 161.1 (J_{CF} 223), 159.2 (J_{CF} 219), 155.6 (J_{CF} 3), 143.7 (J_{CF} 2), 142.1 (J_{CF} 2), 141 (J_{CF} 2), 131.7 (J_{CF} 9), 124.0 (J_{CF} 9), 122.9 (J_{CF} 25), 122.9 (J_{CF} 8), 122.2 (J_{CF} 24), 117.8 (J_{CF} 8), 111.2 (J_{CF} 24), 110.4 (J_{CF} 25). Compound **18**: ^{1}H NMR: δ 8.47 (d, *J* 8.5, 1H), 8.29 (d, *J* 1.9, 1H), 7.99–8.04 (m, 3H), 7.95 (dd, *J* 8.5, 2.8, 1H). ^{13}C NMR: δ 180.9, 156.5, 145.1, 145.0, 144.1, 136.8, 135.3, 134.5, 131.9, 131.4, 126, 124.5, 124.3, 123.9, 118.6. **19**: ^{1}H NMR: δ 8.40–4.82 (m, 2H), 8.13 (dd, *J* 8.5, 2.8, 1H), 8.05–8.08 (m, 2H), 7.92 (d, *J* 8.5, 1H). ^{13}C NMR: δ 180.5, 156.2, 145.2, 144.7, 144.3, 139.5, 137.9, 131.7, 128.9, 126.9, 124.5, 123.9, 122.7, 119.1, 118.7.