Studies of the mechanism of the reduction of different thioxanthen-9-ones

Aneta Kosińska* and Wojciech J. Kinart

Abstract: 2-Propoxythioxanthen-9-one (1), 2-chloro-4-methylthioxanthen-9-one (2) and tributylstannyloxythioxanthene (3) were reduced to 2-propoxythioxanthen (1′), 2-chloro-4-methylthioxanthen (2′) and thioxanthen (3′) using dibutyltin chloro hydride. The mechanism of this reaction involving formation of tributylstannyloxythioxanthyl ketyl radical has been suggested by comparison of products of hydrostannation of three studied thioxanthen derivatives.

Keywords: thioxanthen-9-ones; thioxanthenes; dibutyltin chloride hydride; reduction

1. Introduction

Lucanthone (Miracil D) (Berberian, Freele, Rosi, Dennis, & Archer, 1967; Haidle, Brinkley, & Mandel, 1970; Hirschberg et al., 1968) and hycanthone (Etrenol) (Archer, Pica-Mattoccia, Cioli, Seyed-Mozaffari, & Zayed, 1988; Hirschberg & Weinstein, 1971; Rosi et al., 1967; Ruas, 1972; Turner, Bases, Pearlman, Nobler, & Kabakow, 1975), which are derivatives of thioxanthenone are known as antischistosomal and anticancer agents. With the discovery of curative anticancer activities in animal modes, this series of compounds, like WIN 33377, were advanced into clinical trials (Izbicka, Lawrence, Davidson, Rake, & Von Hoff, 1998; Perni et al., 1998; Stevenson et al., 1999; Wentland et al., 1994).

The exact mechanism of action of these compounds is unknown; however, some members of this family of compounds preferentially inhibit DNA synthesis and mammalian topoisomerase type II. Presumably, thioxanthen-9-ones during such processes undergo reduction into thioxanthenes.

ABOUT THE AUTHORS

We study the catalytic influence of solvation effects and the addition of inorganic salts on: ene reactions of olefins (photo-oxidation and amination); ene reactions of aldehydes and ketones (allylstannylation); metalloene reactions of allyltin compounds; metalloene reactions of tin phenoxides (amination and vinylation); hydrostannylation of ketones and alkynes using tin hydrides; free radical additions leading to formation of new carbon–carbon bonds carried out with Bu3SnH as a coreagent. Additionally, we study the catalytic effect of properties of liquid binary mixtures of organic solvents on photo-oxidation of olefins. These works are linked with studies on physicochemical properties of liquid binary mixtures.

Dr. Wojciech J. Kinart, who is a supervisor of our research group, is the author of 120 papers and three books cited about one thousand times.

PUBLIC INTEREST STATEMENT

Organotin hydrides, due to their high stability, prove to be invaluable reagents in different chemical reactions, such as reduction of functional groups and many others which extend free radical mechanism. Dialkyltin dihydrides R2SnH2 readily react with suitable compounds R2SnX2 where X is an electronegative group, such as halide, carboxylate or sulfonate. This leads to a large variety of hydrides R2SnXH, which are more reactive than simple tributyltin hydride. Thioxanthenones such as these contained in a plant as biologically active Miracil D and Etrenol are compounds widely known because of their anticancer properties and use in the treatment of schistosomiasis. The use of thioxanthenones as sensitizers in manufacturing of paint shows another possibility of application of these compounds. The objective of the present work was to determine the mechanism of reduction of studied thioxanthen-9-ones using dibutyl chloride hydride.
The use of thioxanthenones as sensitizers in production of inks shows another possible application of these compounds. For example, 1-chloro-4-propoxythioxanthen-9-one (Green & Timms, 1993; Green, Timms, & Green, 1991) exhibits higher activity when compared to 4-isopropylthioxanthenone, which is generally regarded as the industrial standard for these systems. In fact, thioxanthen-9-one photosensitizer initiates polymerization of vinyl monomers during such processes.

Yates and Schuster (1984) reported that thioxanthenone triplet is photoreduced by amines via charge-transfer or exciplex intermediate to thioxanthyli ketyl radical. Formed thus, thioxanthenol or ditioxanthyl pinacol are easily oxidized materials. The former is reported to disproportionate on heating to thioxanthene and thioxanthenone. Oehlschlaeger and MacGregor (1950) reported a simple method of reduction of thioxanthenone to 10-thioxanthenol by sodium. Recently, Marcinek, Rogowski, Adamus, Gębicki, and Platz (1996) demonstrated spectroscopically, the intermediacy of the transition radical cation in sequential oxidation processes upon photolysis of thioxanthene. Similar stepwise oxidation processes have also been demonstrated for other NADH analogues (Fakuzami, Tanaka, Fox, & Chanon, 1998). A quantitative oxidation of thioxanthene during such process leads to thioxanthenone. Previously, we have carried out the comparative studies on the hydrostannation of different thioxanthenones by Bu₂SnClH (Kinart, Kinart, Kozak, & Kinart, 2009). However, no clear mechanism of this reduction was presented. In recent years, the organotin hydrides found extensive applications in organic synthesis which involve radical chain reactions in which the stannyl radical is a chain-carrying intermediate. The hydrides R₂SnXH (X = e.g. chloride) can be formed by the comproportionation between diorganotin dihydrides, R₂SnH₂, and the compounds R₂SnX₂ (Scheme 1).

These reactions usually occur readily at room temperature as natural processes in human body involving conversions of anticancer agents.

2. Experimental

2.1. Caution

Although we did not encounter any problem with LiAlH₄, hydrides are potentially hazardous and should be handled with precautions; all reactions should be carried out behind a safety shield inside a fume hood.

Nuclear magnetic resonance spectra were recorded on a Bruker Avance III 600 MHz spectrometer using tetramethylsilane (TMS) as an internal standard.

2.2. General procedure for synthesis and reductions

2-Propoxythioxanthen-9-one (1), 2-chloro-4-methylthioxanthen-9-one (2) were commercial samples. Tributylstannyloxythioxanthene (3) was prepared by reduction of commercial thioxanthen-9-one with LiAlH₄ and azeotropic dehydration carried out in benzene of a mixture of obtained thioxanthen-9-ol with (Bu₃Sn)₂O.

Dibutyltin dihydride was prepared by treatment of dibutyltin dichloride with lithium aluminium hydride in over 50% excess as described by van der Kerk, Noltes, and Luijten (1957). Subsequent ether extraction and distillation gave required dihydride in quantitative yield.

Scheme 1. The hydrides R₂SnXH obtained by the disproportion reaction between diorganotin dihydrides, R₂SnH₂, and the compounds R₂SnX₂.

\[
\text{Bu}_3\text{SnCl}_2 + \text{Bu}_3\text{SnH}_2 \xrightarrow{\text{Bu}_3\text{SnClH}} 2 \text{Bu}_2\text{SnCH}_2
\]
Dibutyltin chloride hydride was prepared by disproportion reaction between dihydride and dibutyltin dichloride (Sawyer & Brown, 1966). The equilibrium was reached within few minutes and it was shifted towards Bu₂SnClH (Scheme 2).

We have carried out reduction 2-propoxythioxanthen-9-one (1), 2-chloro-4-methylthioxanthen-9-one (2) and tributylstannyloxythioxanthene (3) using dibutyltin chloro hydride (Bu₂SnClH).

A typical example of reduction of studied compounds is as follows: 235 mg (1 mmol) of dibutyltin dihydride (Bu₂SnH₂) and 303 mg (1 mmol) dibutyltin dichloride were added to 10 ml of benzene. After 30 min, when the equilibrium leading to formation of Bu₂SnClH was reached, 270 mg (1 mmol) of 2-propoxythioxanthen-9-one (1) was added. The progress of the reaction was monitored by TLC and "H-NMR spectroscopy. After 48 h, the product of the reaction was purified by column chromatography using a mixture of ethyl acetate and petroleum ether (3/7, v/v). The product obtained in quantitative yield was identified as 2-propoxythioxanthene (1'). The same procedure was repeated for 2-chloro-4-methylthioxanthen-9-one (2) and tributylstannyloxythioxanthene (3). It led to formation of 2-chloro-4-methylthioxanthene (2') and thioxanthene (3'), respectively. The products were characterized on the basis of their elemental analysis and "H-NMR spectral analysis (Scheme 3).

Scheme 2. Dibutyltin chloride hydride obtained by the disproportion reaction between dihydride and dibutyltin dichloride.

Scheme 3. Reduction of different thioxanthenones using dibutyltin chloride hydride.
2.3. Spectroscopic data of products are given below

2-Propoxythioxanthene (1′) 1H-NMR (CDCl3, 600 MHz): δ = 1.41–1.48 (2H, m, β-CH2), 4.03 (2H, t, J = 6Hz, α-CH2), 4.09 (2H, s, 9-H), 7.18–7.23 (1H, m, 7-H), 7.23–7.27 (2H, m, 3-H, 6-H), 7.37 (2H, dd, J = 7.4, 1.9 Hz, 4-H, 5-H), 7.48 (2H, dd, J = 7.4, 1.9 Hz, 1-H, 8-H).

2-Chloro-4-methylthioxanthene (2′) 1H-NMR (CDCl3, 600 MHz): δ = 2.32 (3H, s, –CH3), 3.80 (2H, s, 9-H), 7.03–7.07 (4H, m, 1-H, 3-H, 7-H, 8-H), 7.30 (1H, td, J = 7.5, 1.5, 6-H), 7.62 (1H, dd, J = 7.4, 1.9 Hz, 1-H, 8-H).

Thioxanthene (3′) 1H-NMR (CDCl3, 600 MHz): δ = 3.86 (2H, s, 9-H), 7.12–7.20 (2H, m, 2-H, 7-H), 7.20–7.22 (2H, m, 3-H, 6-H), 7.32 (2H, dd, J = 7.4, 1.9 Hz, 4-H, 5-H), 7.44 (2H, dd, J = 7.4, 1.9 Hz, 1-H, 8-H).

Low-resolution mass spectra (MS) of (1′), (2′) and (3′) were taken using chemical ionization (CI) technique with Finningan MAT 95 instrument (source temperature of ca. 200°C, reagent gas-isobutan, accelerating voltage of 4.8 kV). MS (CI) m/z = 255.3, 245.1, 197.1 (M-1) corresponding to above-mentioned thioxanthenes. Calculated values of (M-1) were equal, respectively, to 255.5, 245.7 and 197.3.

4. Results and discussion

The products of reduction of two chosen thioxanthen-9-ones (1), (2) and tributylstannyloxythioxanthene (3) by tributyltin chloride hydride (Bu₂SnClH) have been identified as thioxanthenes (1′), (2′) and (3′).

We have previously (Kinart et al., 2009) observed the analogous course of the reduction for thioxanthen-9-one, 2-chlorothiohanthen-9-one and 1-chlorothioxanthen-9-one by Bu₂SnClH.

We were presently anxious to suggest a definite mechanism of reduction of studied thioxanthen-9-one.

In the purpose to choose or exclude the mechanism involving formation of ketyl radical during such reduction, we have reduced thioxanthen-9-one to thioxanthen-9-ol using LiAlH₄. Further azeotropic dehydration in benzene of a mixture of thioxanthen-9-ol with bis(tributyltin) oxide gave 9-tributylstannyloxythioxanthene. Its reduction with Bu₂SnClH led directly to thioxanthene. It seems to indicate the formation of the ketyl radical as an intermediate product, similarly as it has been reported by Yates and Schuster (1984) during photoreduction of thioxanthenones.

Funding
Our project has been financed from the University of Lodz Grant.

Author details
Aneta Kosińska1
E-mail: kosinskaneta@wp.pl
Wojciech J. Kinart1
E-mail: wkinart@wp.pl
1 Department of Organic Chemistry, University of Lodz, Tamka 12, 91-403 Lodz, Poland.

Citation information
Cite this article as: Studies of the mechanism of the reduction of different thioxanthen-9-ones, Aneta Kosińska & Wojciech J. Kinart, Cogent Chemistry (2015), 1: 1064194.

References
Archer, S., Pica-Mattoccia, L., Cioli, D., Seyed-Mozaffari, A., & Zayed, A.-H. (1988). The preparation, antischistosomal and antitumor activity of hycanthone and some of its congeners. Evidence for the mode of action of hycanthone. Journal of Medicinal Chemistry, 31, 254–260. http://dx.doi.org/10.1021/jm003960a040
Berberian, D. A., Freele, H., Rosi, D., Dennis, E. W., & Archer, S. J. (1967). Schistosomicidal activity of lucaanthone hydrochloride, hycanthone and their metabolites in mice and hamsters. The Journal of Parasitology, 53, 306–311. http://dx.doi.org/10.2307/3276581
Fukuzumi, S., Tanaka, T. (1998). NAD(P)H, NAD+, and analogues. In M. A. Fox & M. Chanon (Eds.), Photoinduced electron transfer (Part C, pp. 578–635). Amsterdam:Elsevier.
Green, W. A., & Timms, A. W. (1991). Proceedings of Radtech Europe (p. 636). Edinburgh: Radtech Europe.
Haidle, C. W., Brinkley, B. R., & Mandel, M. J. (1970). Effect of Miracil D on marker frequency ratio and cytotoxicity in Bacillus subtilis. Journal of Bacteriology, 102, 835–842.
Hirschberg, E., & Weinstein, I. B. (1971). Comparative ability of hycanthone and Miracil D to interact with DNA. Science, 174, 1147–1148. http://dx.doi.org/10.1126/science.174.4014.1147
Hirschberg, E., Weinstein, I. B., Gersten, N., Marner, E., Finkelstein, T., & Carchman, R. (1968). Structure-activity studies on the mechanism of action of Miracil D. Cancer Research, 28, 601–607.

Izbicka, E., Lawrence, R., Davidson, K., Rake, J. B., & Von Hoff, D. D. (1998). Effects of SW 33377, SW 68210 and SW 71425 thioxanthenones on in vitro colony formation of freshly explanted human tumor cells. Investigational New Drugs, 16, 221–225. http://dx.doi.org/10.1023/A:1006152100299

Kinart, W. J., Kinart, A., Kozak, M., & Kinart, C. M. (2009). Studies on the reduction of different thioxanthenones by dibutyltin chloride hydride. Main Group Metal Chemistry, 32, 247–252.

Marcinek, A., Rogowski, J., Adamus, J., Gebicki, J., & Platz, M. S. (1998). Sequential electron–proton–electron transfer in the radiolytic and photochemical oxidation of thioxanthene and xanthene. The Journal of Physical Chemistry, 102, 13539–13543. http://dx.doi.org/10.1021/jp9804040

Oehlschlaeger, H. F., & MacGregor, I. R. (1950). An improved synthesis of 10-thioxanthenol. Journal of the American Chemical Society, 72, 5323–5333. http://dx.doi.org/10.1021/ja011670z

Perni, R. B., Wentland, M. P., Huang, J. L., Powles, R. G., Aldous, S., Klingbell, K. M., ... Coughlin, S. A. (1998). Synthesis and antitumor activity of 4-aminomethylthioxanthone and 5-aminomethylbenzothiopyranodazole derivatives. Journal of Medicinal Chemistry, 41, 3645–3654. http://dx.doi.org/10.1021/jm9708083

Rosi, D., Peruzzotti, G., Dennis, E. W., Berberian, D. A., Freele, H., Tullar, B. F., & Archer, S. (1967). Hycanthone 1 a new active metabolite of lucanthone 2. Journal of Medicinal Chemistry, 10, 867–876. http://dx.doi.org/10.1021/jm003170a025

Ruus, A. (1972). Hycanthone in 1035 cases of vesical schistosomiasis. Central African Journal of Medicine, 18, 109–112.

Sawyer, A. K., & Brown, J. E. (1966). Reactions of n-butyltin hydrides with n-butyltin halides. Journal of Organometallic Chemistry, 5, 438. http://dx.doi.org/10.1016/S0022-328X(00)82378-5

Stevenson, J. P., DeMaria, D., Reilly, D., Purvis, J. D., Graham, M. A., Lockwood, G., ... O’Dwyer, P. J. (1999). Phase I/pharmacokinetic trial of the novel thioxanthone SR233377 (WIN33377) on a 5-day schedule. Cancer Chemotherapy and Pharmacology, 44, 228–234. http://dx.doi.org/10.1007/s002800050971

Turner, S., Bases, R., Pearlman, A., Nobler, M., & Kabakov, B. (1975). The adjuvant effect of lucanthone (Miracil D) in clinical radiation therapy. Radiology, 114, 729–731. http://dx.doi.org/10.1148/114.3.729

van der kerk, G., Noltes, J. G., & Luijten, L. G. A. (1957). Investigations on organo-tin compounds. VIII. Preparation of some organo-tin hydrides. Journal of Applied Chemistry, 7, 366–369.

Wentland, M. P., Perni, R. B., Powles, R. G., Hlavac, A. G., Matess, K. C. P., Corbett, T. H., ... Rake, J. B. (1996). Anti-solid tumor efficacy and preparation of N-[1-[(diethylamino)ethyl]amino]-9-oxo-9H-thioxanthene-4-yl]methylmethanesulfonamide (win 33377) and related derivatives. Bioorganic & Medicinal Chemistry Letters, 4, 609–614. http://dx.doi.org/10.1016/S0960-894X(01)80164-5

Yates, S. F., & Schuster, G. B. (1984). Photoreduction of triplet thioxanthone by amines: Charge transfer generates radicals that initiate polymerization of olefins. The Journal of Organic Chemistry, 49, 3349–3356. http://dx.doi.org/10.1021/jo00192a019