

Oxidation Behaviour of Benzothiazine

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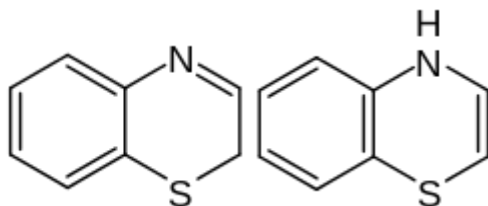
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ABSTRACT: Benzothiazine is a heterocyclic compound consisting of a benzene ring attached to the 6-membered heterocycle thiazine. The name is applied to both the 2H- and 4H-isomers of the molecule.

2,1-Benzothiazine, a type of benzothiazines was first reported in the 1960s. Subsequently, their preparation and intensive biological and physiological studies have been reported. In recent years, 2,1-benzothiazines have been of enormous interest to synthetic chemists. An enantioselective synthesis of such benzothiazines has been developed by Harmata and Hong who have formulated transformations of these compounds designed to target chiral, non-racemic building blocks as well as natural products.

KEYWORDS: benzothiazine, heterocyclic, oxidation, behavior, chiral, isomers, chemists, enantioselective

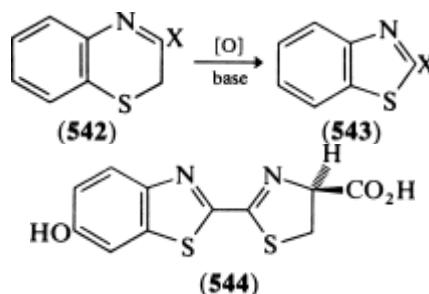
INTRODUCTION

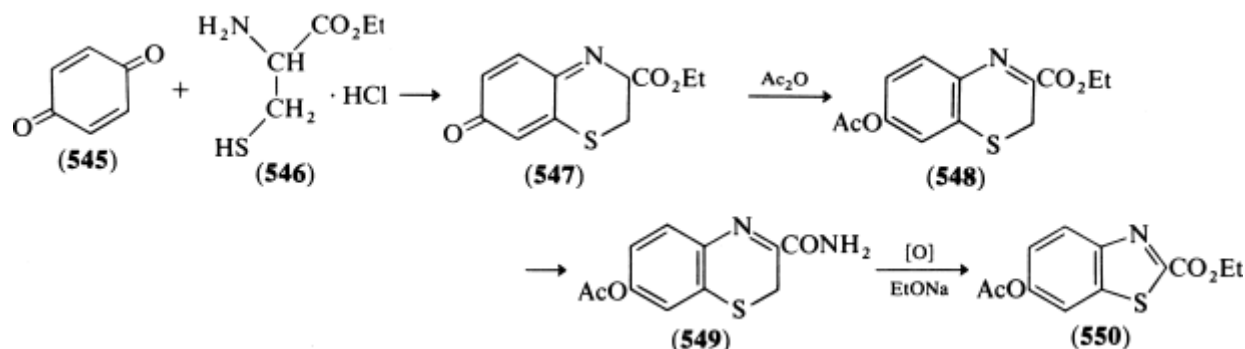


3-H ISOMER

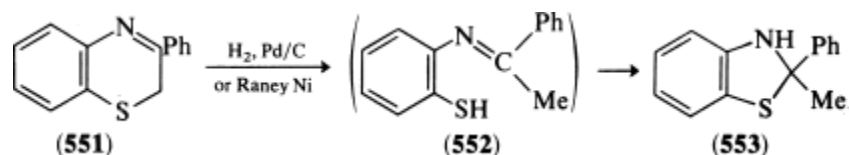
4-H ISOMER

Benzothiazines may rearrange into benzothiazoles by oxidation in the presence of a base¹. This type of synthesis was prompted by the suggestion that the biosynthesis of firefly luciferin could result from a similar rearrangement of the benzothiazine formed by the condensation of p-benzoquinone and cysteine². The reaction of p-benzoquinone with ethyl cysteinate hydrochloride affords an intermediate which on acetylation rearranges to 7-acetoxy-1,4-benzothiazine ester. Oxidation of the corresponding amide with potassium ferricyanide³ in the presence of NaOEt gives 2-ethoxycarbonyl-6-hydroxybenzothiazole.⁴



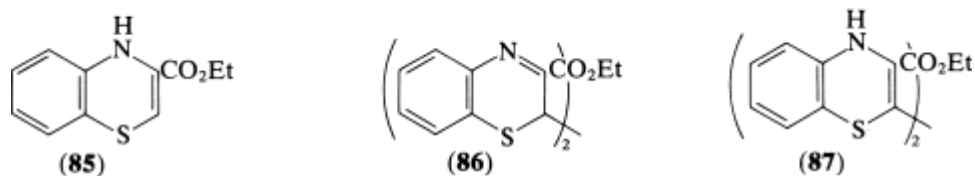
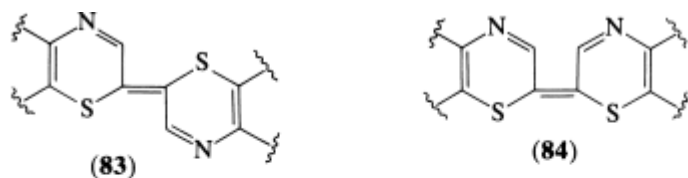


Catalytic hydrogenation of 3-phenyl-2H-1,4-benzothiazine in the presence of palladium-charcoal or Raney nickel affords 2-methyl-2-phenyl-2,3-dihydrobenzothiazole. The reaction is probably initiated by the hydrogenolysis of the C-S bond of ⁵resulting in the intermediate thiophenol ⁶which cyclizes to the final benzothiazoline ⁶.

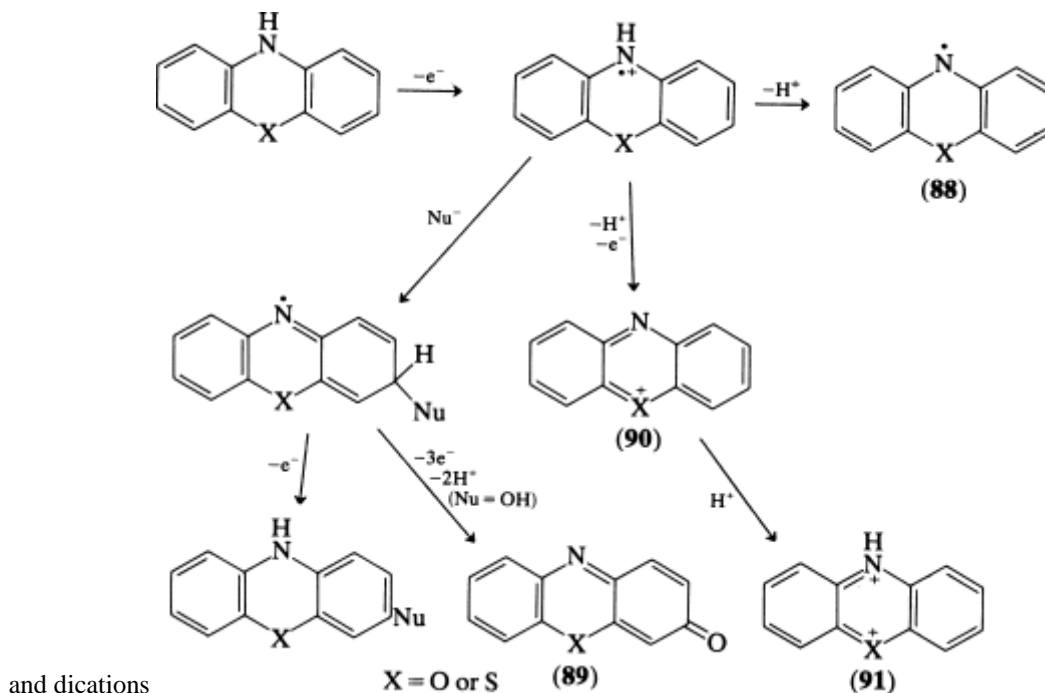


II.DISCUSSION

2H-1,4-Thiazines and benzothiazines undergo oxidation to dehydro dimers and which are of considerable interest as they are the parent chromophores of the trichosiderin (trichochrome) pigments which occur in mammalian red hair and in the feathers of some birds ⁷. In the case of monocyclic thiazines, reagents such as nitrobenzene or picric acid are required, but air oxidation is sufficient in the bicyclic series. It is curious that whereas aerial oxidation of the ester gives both the dehydro dimers and ethyl azodicarboxylate only yields the tautomer ⁸.

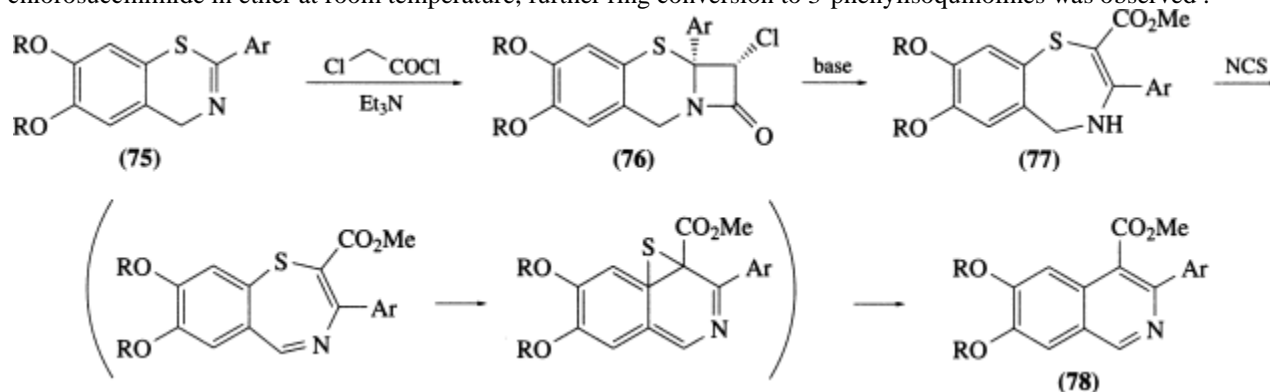


The initial products of the oxidation of phenoxazines and phenothiazines are cation radicals. Reagents such as ferric chloride are effective, and a solution of phenoxazine in concentrated sulfuric acid allowed to stand for several days shows an ESR spectrum compatible with the presence of such a radical cation. On neutralization, or basification, the radical cations are deprotonated to neutral radicals which may couple to form high molecular weight species linked through positions 3 and 10' or through positions 10 and 10⁹. In aqueous media the initially formed radical cations may react with water and the products undergo further oxidation to phenoxazin- or phenothiazin-3-ones but if more reactive nucleophiles are present other 3-substituted derivatives are produced. For example, the radical cations of N-substituted phenoxazines can be quenched with bromide, isothiocyanate or nitrite ions to give the corresponding 3,10-disubstituted compounds and the dyestuff methylene blue is obtained by the oxidation of phenothiazine in the presence of dimethylamine. In strongly acidic media further oxidation of the radical cations is possible, leading to cations ¹⁰



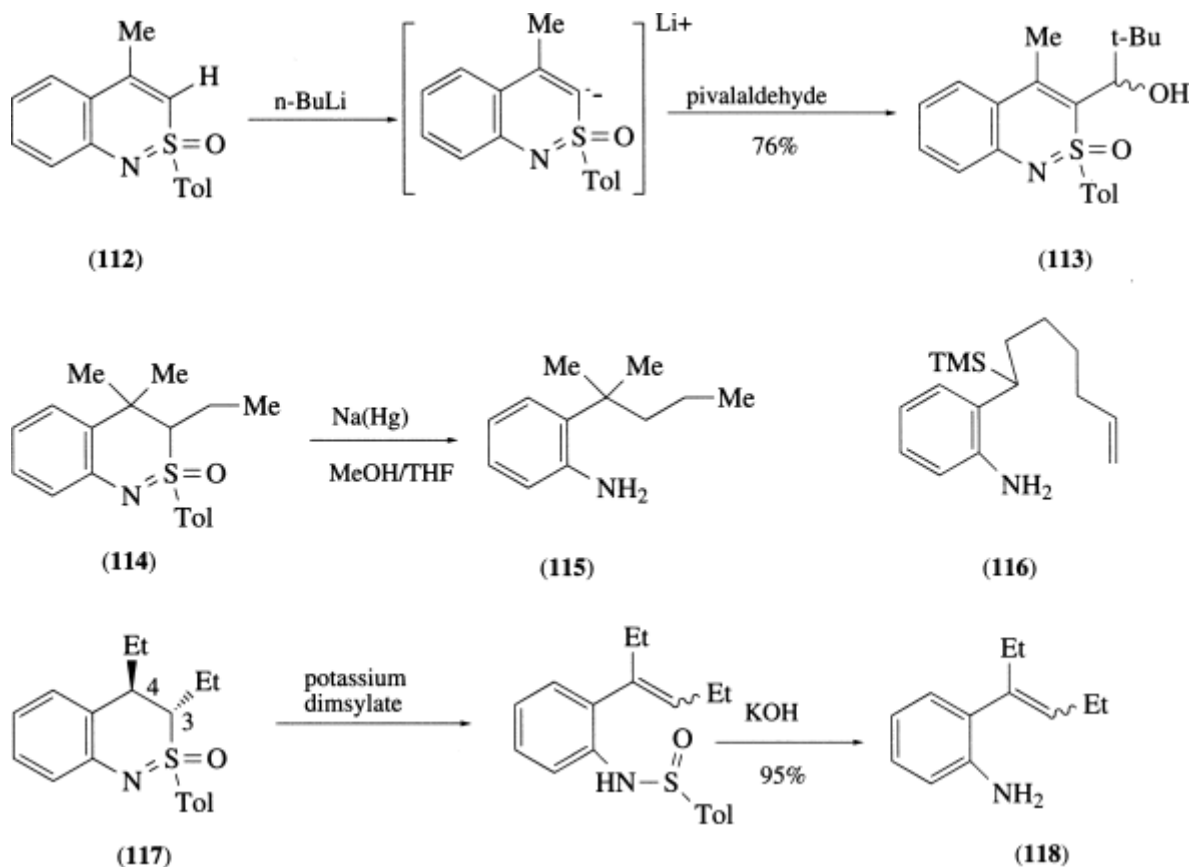
III.RESULTS

2-Aryl-4H-1,3-benzothiazines reacted with chloroacetyl chloride in the presence of triethylamine to form the β -lactam derivative which underwent rearrangement in the presence of base to form 4,5-dihydro-1,4-benzothiazepine (64% yield). When it was stirred with N-chlorosuccinimide in ether at room temperature, further ring conversion to 3-phenylisoquinolines was observed.¹¹



IV.CONCLUSIONS

Since 1988 the chemistry of 2-aryl-2,1-benzothiazine 2-oxides has been studied in some detail.¹² The benzothiazine oxide can be smoothly deprotonated by n-BuLi, and the resulting sulfoximine-stabilized anion can be trapped by an assortment of electrophiles. However, none of the alkylation reactions showed any diastereoselectivity (e.g., was obtained as a 2.5/1 isomeric mixture; no allylic deprotonation was observed).¹³



The 3,4-dihydro-2,1-benzothiazines undergo some useful synthetic transformations. Treatment of the benzothiazine with sodium amalgam yields the 2-alkylaniline by reductive desulfonation. Since benzothiazines such as can be prepared from anilines,¹⁴ this reaction constitutes a regioselective ortho-alkylation of anilines. This reaction sequence can also be used to prepare highly substituted anilines such as The benzothiazine can be converted into the corresponding 2-alkenyl amine upon treatment with potassium dimslyate followed by saponification.¹⁵ Even though this route to 2-alkenylanilines is general and regioselective, it is not stereoselective. The lack of stereoselectivity is probably due to the loss of stereochemical integrity at C-3 before the irreversible deprotonation of C-4 leading to ring cleavage .

In the mid-1990s, a related sequence of reactions has been used for the regioselective preparation of 2-allyl and 2-alkenyl anilines from 2,1-benzothiazines¹⁶ .

REFERENCES

1. Braun, J. Chem. Ber. 1923, 56,2332.
2. Abe, K.; Yamamoto, S.; Matsui, K. Yakagaku zasshi 1956, 76, 1058: Chem. Abstr. 1957, 51, 3499.
3. Soler, J. E. U. S. Patent 1985, 4,563,452.
4. Suzuki, A.; Yajima, Y; Yokoyama, S.; Matsuoka, Y; Irimajiri, S. Japan Pharmacol. Ther 1994, 22, 221: Marfat, A. Annual Drug Data report 1987, p 202: U. S. Patent 1985, 4,551,452.
5. Turck, D.; Busch, U.; Heinzl, G.; Narjes, H.; Nehmiz, G. Clin. Drug Invest. 1995, 9, 270: Engelhardt, G. Brit. J. Rheumatol. 1995, 34, 90.
6. Caruso, I; Montrone, F.; Boari, L. Adv. Ther. 1994, 11, 132.
7. Lombardino, J. G.; Wiseman, E. H.; Mclamore, W. J. Med. Chem. 1971, 14, 1171.
8. Kwon, S. K.; Park, M. S. Arzneim-Forsch/DrugRes. 1996, 46(II), 966.
9. Park, M. S. J. Korean Chem. Soc. 1998, 42(6), 657.
10. Kwon, S. K.; Park, M. S. Bull. Korean Chem. Soc. 1992, 13(5), 526.



11. Lalezari, I. J. Heterocyclic. Chem. 1985, 22, 741.
12. Kwon, S. K.; Jung, H. W.; Park, M. S. Korean J. of Med. Chem. 1995, 5(2), 166.
13. Sulfostyryl (2,1-benzothiazine 2,2-dioxide). I. Preparation and reactions of 3,4-dihydrosulfostyryl. Loev, B.; Kormendy, M.F. J. Org. Chem. 1965, 30, 3163.
14. Recent Progress in the Chemistry of 2,1-Benzothiazines. Hong, X.; Harmata, M. Progress in Heterocyclic Chemistry, Chapter 1, G. W. Gribble and J. A. Joule, eds, Pergamon Press, Vol 19, pp 1-43 (2008)
15. The Intramolecular, Stereoselective Addition of Sulfoximine Carbanions to α , β -Unsaturated Esters. Harmata, M.; Hong, X. Journal of the American Chemical Society, 2003, 125(19), 5754-5756.
16. Benzothiazines in Synthesis. A Total Synthesis of Pseudopteroxazole. Harmata, M.; Hong, X. Organic Letters, 2005, 7(16), 3581-3583.