SUMMARY

The prostaglandins (PGs) form a class of natural products with diverse and potent biological activities. The natural PGS are unsaturated hydroxylated fatty acids, all derivatives of a parent compound called prostanoic acid (**Figure 1**). As yet, their precise physiological role has not been clearly defined, but their potency and activity in many apparently unrelated biological systems have awakened the interest of scientists of various disciplines. Indeed, PG are associated with most mammalian tissues and implicated in an ever-increasing number of physiological systems [1].

From the historical point of view, in 1930 Kurzrok and Lieb showed that the human semen could induce strong contractions or relaxations when applied to a human uterus [2]. A few years later, Von Euler and Goldblatt demonstrated independently the presence of a vasodepressor agent and a stimulating factor of muscles in human seminal plasma and sheep vesicular glands [3]. Von Euler indicated that the biological activity was due to a lipid soluble material with acidic properties and called it "prostaglandin"[4].

About 30 years elapsed between the discovery of the biological activity of PG and the structure elucidation of two of them. The reasons why this field remained dormant for so long are multiple and in part are due to the technical difficulties encountered earlier in the isolation of natural PG. In addition, the dramatic development of antibiotics and hormone therapy made during the past 30 years somehow caused PG research to fall into oblivion. In 1957, Bergstrom and Sjovall isolated the crystalline PGE_1 and $PGF_{1\alpha}$ from sheep vesicular seminal extracts [5]. A short time later, Bergstrom, Sjovall, and Samuelsson were able to differentiate and they isolate 13 different substances. It was only after this isolation and structure work when PGS were shown to be biologically active entities that the field came to life. Previously their biological properties had been attributed to other known substances [6].

Natural occurring PG may be regarded as derivatives of prostanoic acid, an organic acid with a substituted cyclopentane unit [7]. The natural PG are divided into three "series" namely, the first which presents only one double bond between position 13 and 14, the second with an addition olefinic bond between C-5 and C-6, and the last with a third double bond located between C-17 and C-18. Furthermore, natural PG form two major groups, Primary and Secondary. In primary PG including the members of the E and F families, as shown in Figure **1**. Where as the members of the A, B, C, D, G and H

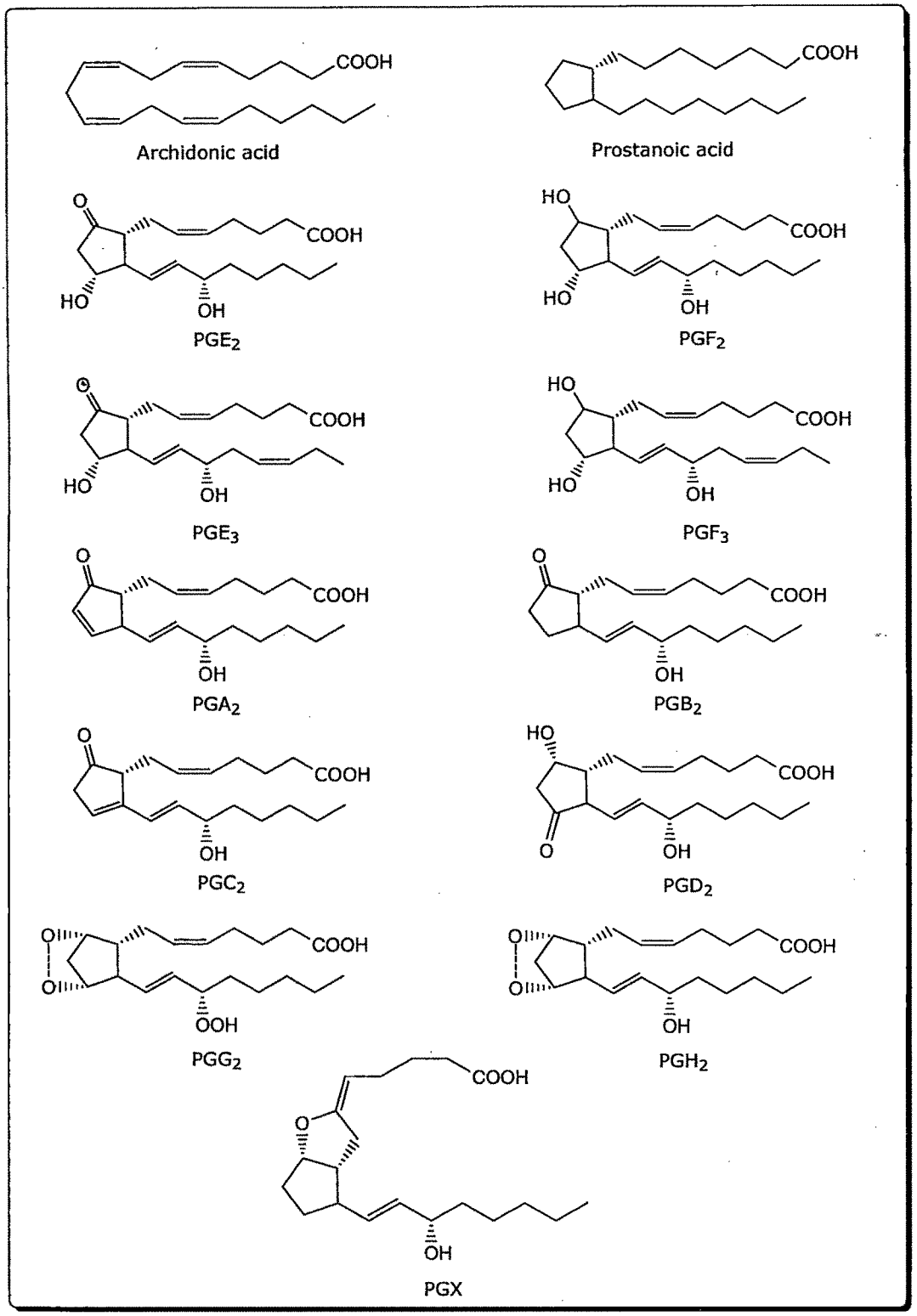

COOH
Archidonic acid
COOH
Prostanoic acid
O
COOH
HO
OH
PGE2
HO
COOH
HO
OH
PGF2
O
COOH
HO
OH
PGE3
HO
COOH
HO
OH
PGF3
O
COOH
OH
PGA2
O
COOH
OH
PGB2
O
COOH
OH
PGC2
HO
COOH
O
OH
PGD2
O
O
COOH
OOH
PGG2
O
O
COOH
OH
PGH2
COOH
O
OH
PGX

Figure 1

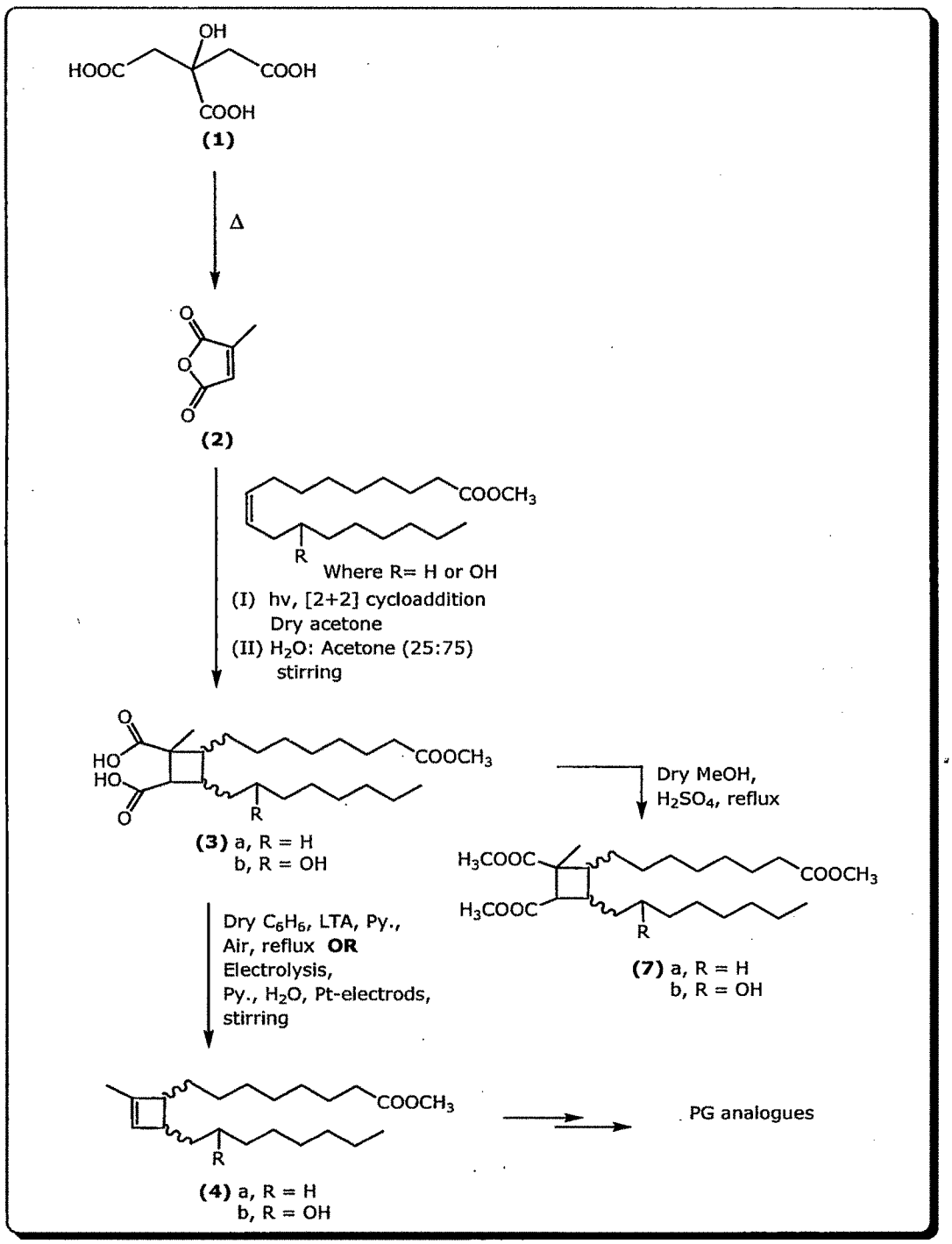
families forming the Secondary PG, some of which are shown in the **Figure 1**. The six primary PG present an oxygen at position 9 (ketone in E series, hydroxyl in F series) and C-11 & C-15 (α-hydroxyl groups), as well as a trans double bond between C-13 & C-14. Rules for the nomenclature have been proposed [7] using the prostane skeleton as the basic unit. From time to time, this nomenclature will be mentioned. For example, PGA_2 is called 5*Z*,13*E*,15(*S*)-hydroxy-9-oxoprosta-5,10,13-triene-1-oic acid, although the commonly accepted abbreviation PGA_2 will be used more often for convenience.

PG are known to be widely distributed in mammals [8], and van Drop *et al.* [9] have reported the comparative aspects of PG biosynthesis in different animals. Prostaglandins have been found in the urinary bladder [9] and intestine [10] of the frog, as well as in the gastrointestinal tract of the shark *Triakis scyllia* [11]; PG synthetase has been found in mussels and lobsters [9]. In addition, PG have been identified in the testes and semen of Teleosts [12]. Prostaglandins mainly A_2 and E_2 have also been isolated in rather large amount from animals as simple as the marine soft coral *Plexaura homomalla* (Esper) [13].

In mammals, PG found in low concentrations in numerous tissues and fluids, as well as in a large number of organs, such as in the iris of eye, the brain, the thymus, the bronchials, the lungs, the human seminal plasma, the seminal fluid, the ovary, and the uterus. After appropriate stimulation, PG identified in the intestine, the adrenal glands, the stomach, the kidneys, the nervous tissues, etc. However, the total PG production in the adult human is only of the order of 1 to 2 mg per 24 hours [14].

A major difficulty in the biological evaluation and practical application of prostaglandins (PG) was due to the fact that the supply of primary PG from natural sources, such as sheep vesicular glands, was not sufficient to permit broad testing. In spite of the fact that the total synthesis of PG constitutes a challenge for organic chemists, numerous conceptually different synthetic routes have been explored with considerable success. A primary difficulty that one faces in their synthesis is the introduction in the same molecule of a number of functional groups of different nature. Second, the stereochemistry of the PG, in extenso the geometry of the double bonds, the configuration of the chains at C-8 & C-12 and the configuration of hydroxyls at position 9,11 &15, is critical for the bioactivity. In addition, five asymmetric centers are present in

many natural PG and their incorporation into a total synthesis scheme constitutes a formidable objective, as most chemical reactions afford mixtures of isomers.



Scheme 1

The **first chapter** provides brief introduction of prostanoid, historical background, nomenclature, structure and stereochemistry, natural occurrence, biological properties and various reaction sequences in total synthesis of different class of prostaglandins.

In spite of the fact that the total synthesis of PG constitutes a challenge for organic chemists, numerous conceptually different synthetic routes have been explored with considerable success. It is obvious from the literature that many of the approaches towards prostaglandins are multi-step sequences involving use of complex reagents and tedious work up procedures. In addition, some of the routes also lack adaptabilities on large scale operations. One of the earliest known approaches to prostanoids from acyclic precursors involves an aldol condensation to create cyclopentane ring. However, this cyclisation approach met with some of the problems like regioselectivity, stereochemistry at the ring substitution and selective functional group protection.

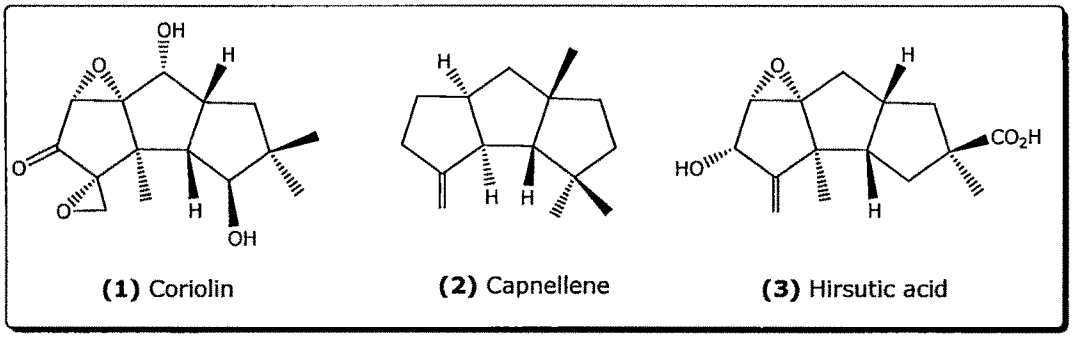
It is clearly seen from the various routes that we have described herein for the synthesis of PGs, majority of methods proceed via bicyclic lactone intermediate and are multi step sequences. It was therefore desired to design and development of a general, short procedure for the rapid acquisition of natural PG framework via [2+2] cycloaddition and oxidative decarboxylation of the resulting diacid using cheap and easily available starting materials like Citric acid and Methyl oleate or Methyl ricinoleate.

Our efforts directed towards realization of the above objectives are described in the **second chapter** of this thesis.

Third chapter describes novel one-pot synthesis of acetoxy-2,4-cyclohexadienones from some substituted phenols. Polyquinane is a generic name given to carbocyclic frames composed of fused five membered rings that constitutes an important class of sesquiterpenoids. Since their discovery, polyquinane natural products have generated a worldwide interest among organic chemists due to their unique and fascinating molecular architecture and promising biological activity [15,16] Literature survey reveals over hundred such natural products isolated from plants [17], marine organisms [18], fungi and insects.[19,20]

The fact that polyquinanes exhibit diverse biological activity has generated a flurry of activity in their chemistry. For example, coriolin **(1)** **(Figure 2)** shows antitumor

and antibacterial activitiy[20], capnellene (**2**) has been suggested to act as a chemical defense agent to inhibit the growth of microorganisms[18] while hirsutic acid (**3**) is shown to possess antibiotic properties.[21,22] Though a variety of methods have been developed for the construction of tricyclopentanoid framework, most of them are target specific, lacking adaptability and involve multi-step sequences. [23]

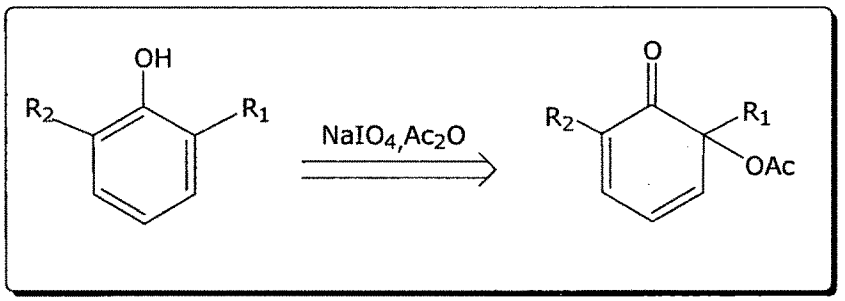


(1) Coriolin **(2)** Capnellene **(3)** Hirsutic acid

Figure 2

Cyclohexadienones, well known intermediates in the literature; only a few methods are reported for their preparation. The oxidation of phenols with lead-tetraacetate, known as "Wessely oxidation"[24] is a generally used method for their preparation. However, it often proceeds in low yields and furnishes a mixture of products depending upon the nature of the substituents on the aromatic ring.[(14)] Alternatively, it can also be prepared in the dimeric form by the periodate oxidation of phenols as investigated by Adler *et al.*[25] followed by acetylation of 3° hydroxy groups using Fritz-Schenk reagent.[26] Occasionally, diacyl peroxide and trifluoro-peroxyacetic acid have also been used for their preparation. Wessely oxidation gives acetoxycyclohexadienones in one step albeit in low yields. On the other hand, Adler's method gives relatively better yields but results in the formation of a dimeric compound, which needs to be acetylated to furnish corresponding diacetate dimer. The dimeric diacetate requires being pyrolzed to furnish the corresponding acetate, which results in lower overall yield.

During our search for a better method, we explored the reaction of various type of substituted phenols with periodate in acetic anhydride medium. It was thought that the oxidative acetylation of phenol would give the corresponding acetoxy-cyclohexadienone directly in one step with better yield, as depicted in following **Scheme 2.**



Scheme 2

Structures of all the compounds were readily established through its spectral and analytical data. Melting points were recorded in open capillary tubes and are uncorrected. Ultraviolet spectra were recorded on a Perkin-Elmer Lambda-19 Spectrometer. Infrared spectra were recorded on a Perkin-Elmer PC-16 FTIR Spectrophotometer. PMR (300/400 MHz) spectra and ^{13}CMR (75.5 MHz) were recorded either on a Bruker-300-FT-NMR or on a Bruker-AC-400-FT-NMR using $CDCl_3$ as solvent containing tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu QP-5050-A mass spectrometer. Microanalyses were performed on a Perkin-Elmer 2400 series II Laser instrument. Column chromatography was performed using Acme's silica gel (60–120 mesh size) and the elution was done using mixture of light petroleum and ethyl acetate. The percent yields are reported based on the isolated material after column chromatography. Thin layer chromatography was performed using Acme's silica gel for TLC and spots were visualized in iodine vapor.

The present method gives better yields of the cyclohexadienones in one step from the corresponding phenols. Moreover it also avoids the use of the tedious Fritz-Schenk reagent, which selectively acetylates the 3° hydroxyl groups.

The **fourth chapter** deals with synthesis and characterization of novel photostabilizing surfactants. Many organic compounds when exposed to sunlight are prone to undergo chemical reactions subsequent to electronic excitations.[27] Therefore, need of protecting material against solar irradiation in outdoor applications has motivated numerous activity in the area of photodegradation and its mechanisms.[28,29] The damaging UV radiation is responsible for the discoloration of dyes and pigments, weathering, yellowing of plastics, loss of gloss and mechanical properties (cracking), sunburnt skin,

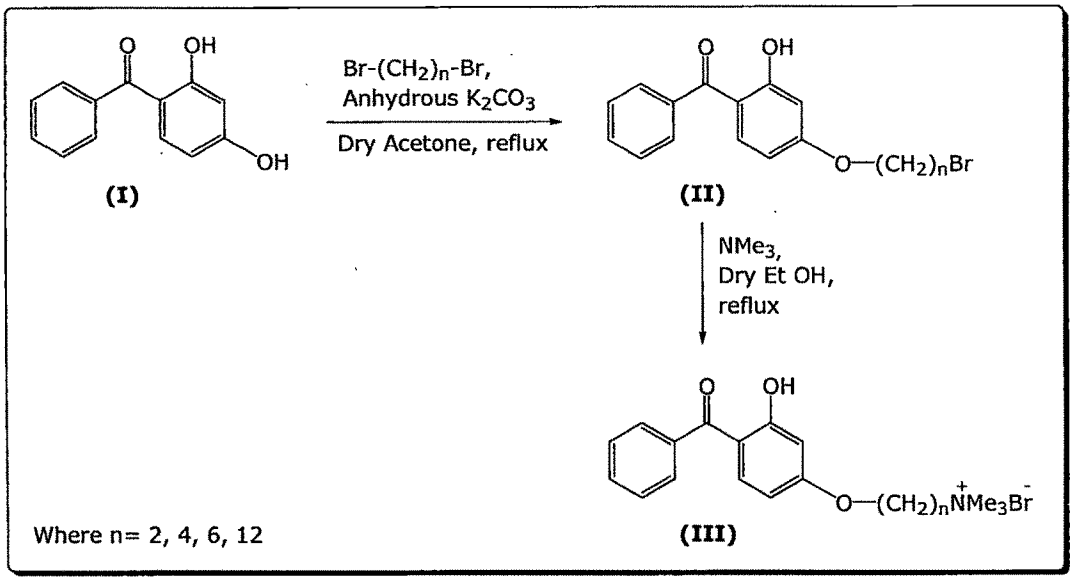
degradation of pesticides/bio-pesticides and other problems associated to UV light. Paints, plastics, pesticide, wood and cosmetic manufacturers have a great interest in offering products that remain unaltered for long periods of time under the worst light exposure conditions.[30]

Sensitivity to sunlight/UV light, limits the use of some synthetic or natural pesticides in agriculture. Classical approaches to overcome this problem generally involve chemically modified molecular structures of the pesticides or use of the UV absorbing molecules in the formulations. However, in the former method any chemical modification in structure may seriously affect the pesticidal activity of that compound and may cause ecological problems.[31] Therefore, the latter method, which is free from the above-mentioned disadvantages, is more suitable to extend the environmental life of the pesticides.[32] In order to offer an effective protection against UV irradiation, one of the requirements for the UV absorber molecules is the ability of transforming the absorbed radiation energy into less damaging thermal energy *via* photophysical process.[28] The four most important UV absorber classes are the hydroxyphenyl-benzotriazoles (BTZ), hydroxyphenyl-s-triazines (HPT), hydroxybenzophenones and oxanilides.

Aim of this work is to prepare novel photostabilizing surfactants with water solubility and effective photostability by simple reaction sequences. Structural modification of 2,4-dihydroxy benzophenone **(I)** led to the water-soluble quaternary ammonium compounds **(III)** via monoalkylation of **(I, Scheme 3)**.

During photostabilization study the standard solutions of pure Disulfoton with and without individual UV absorbers in methanol, placed in a Pyrex immersion–well type of a photochemical reactor were irradiated individually using a high-pressure mercury vapor lamp for 12 h. The irradiated solutions were analyzed for the remaining Disulfoton content by analytical HPLC. Control samples were irradiated and analyzed similarly.

We have presented herein the idea of designing and synthesizing the novel water soluble compounds having properties of photostabilizers. Further research in this direction can lead to development of more useful and general compounds of interest in this class.



Scheme 3

TABLE II: Percentage recovery of Disulfoton in presence and absence of UV absorber on exposure to UV radiation in methanol after 12 hrs.
(Disulfoton: UV absorber, 1:1 mole ratio)

Sr. No.	Samples	% Recovery
1	Disulfoton (no photostabilizer)	61.80
2	($C_{18}H_{22}O_3$ NBr)	87.44
3	($C_{20}H_{26}O_3$ NBr)	84.07
4	($C_{22}H_{30}O_3$ NBr)	85.86
5	($C_{28}H_{42}O_3$ NBr)	86.45

Rreferences

1. von Euler, U.S. (1971). *Ann. N. Y. Acad. Sci.* **180**, 6.
2. Kurzrok, R., and Lieb, C.C. (1930). *Proc. Soc. Exp. Biol. Med.* **26**, 268.
3. Goldblatt, M.W. (1933). *J. Soc. Chem. Ind., London 5*, 1056; (1935). *J. Physiol. (London)* **84**, 208.
4. von Euler, U.S. (1934). *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.* **175**, 78; (1936). *J. Physiol. (London)* **88**, 213.
5. Bergstrom S., and Sjovall, J. (1957). *Acta Chem. Scand.* **11**, 1086; (1960). **14**, 1693.
6. Bergstrom S. (1967). *Science* **157**, 382; Bergstrom, S., and Samuelsson, B. (1968). *Endeavour* **27**, 109.
7. Nelson, N.A. (1974). J. Med. Chem. 17, 911; Ardersen, N. (1971). *Ann. N.Y. Acad. Sci.* **180**, 14, 24..
8. Colbert, J.C. (1973). "Prostaglandins. Isolation and Synthesis." Noyes Data Corp., Park Ridge, New Jersey.
9. van Drop, D.A. (1975). *Proc. K. Ned. Akad. Wet.* **84**, 34; *Proc. Nutr. Soc.* **34**, 279; Christ, E.J., and van Drop D.A. (1972). *Biochim. Biophys. Acta.* **270**, 537.
10. Suzuki, T., and Vogt, W. (1965). *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.* **252**, 68.
11. Ogata, H., and Nomura, T. (1975). *Biochim. Biophys. Acta* **84**, 388.
12. Nomura, T. Ogata, H., and Itoh, M. (1973). *Tohoku J. Agric. Res.* **24**, 138.
13. Weinherimer, A.J., and Spraggins, R.L. (1969). *Tetrahedron Lett.* p.5185; Schneider, W.P., Hamilton, R.D., and Rhuland, L.E. (1972). *J. Am. Chem. Soc.* **94**, 2122.
14. Samuelsson, B. (1965). *J. Am. Chem. Soc.* **87**, 3011; Hamberg, M., and Samuelsson, B. (1973). *Proc. Natl. Acad. Sci. U.S.A.* **70**, 899.
15. Hanssen, H. P.; Abraham, W.R. (1988). *Tetrahedron.* **44**, 2175; Ayer, W.A.; Browne, L.M. (1981). *Tetrahedron* **37**, 2199.
16. Singh, V.K.; Thomas, Beena.(1992). *J. Chem. Soc., Chem. Commun.*211.
17. Zalkow, L.H.; Harris, R. N.; Van der Veen, D.; Bertrand, J. A.(1980)*J. Chem.*

Soc., Chem. Commun. 420; Bohlman, F.; Jakupovic, J.(1980). *Phytochemistry* **19**, 259.

18. Shaikh, Y.M.; Singy, G.; Kaisin, M.; Eggert, H.; Djerassi, C.; Tursch, B.; Daloze, D.; Braeckman, J. C.(1976). *Tetrahedron* **32**, 1171.
19. Martin, D.G.; Slomp, G.; Mizsak, S.; Duchamp, K.J.; Chidester, C.G. (1970). *Tetrahedron Lett* 4901.
20. Shuji, T.; Naganawa, H.; Izuma, H.; Takita, T.; Umezawa, H.(1971). *Tetrahedron Lett.*1955.
21. Comer, F.W.; McCapra, F.; Qureshi, I.H.; Scott, A.I.(1967). *Tetrahedron* **23**, 4761.
22. Paquette, L.A.(1979). *Topics in Current Chemistry*; Springer-Verlag, **79**, 41.
23. Curran, D.P.; Abraham, A.C.; Liu, H.(1991). *J. Org. Chem.***56**, 4335.
    Plamondon, L.A.; Wuest, J.D. (1991). *J. Org. Chem.* **56**, 2076.
    Mehta, G.; Kara, S.R. (1991). *J. Chem. Soc., Chem. Commun.* 1367.
24. Zbiral, E.; Wessely, F.; Lahrmann, E. (1960). *Mh. Chem.* **91**, 331.
25. Adler, E.; Brasen, S.; Miyake, H., *Acta. Chem. Scand.*; **1971**, 25, 2055.
    Adler, E.; Dahlen, J.; Westin, G. (1960). *Acta. Chem. Scand.***14 (7)**, 1580.
26. Fritz, J. S.; Schenk, G. S. (1959). *Anal. Chem.* **31**, 1808.
27. Heller, H. J. (1969). *Eur. Poly. J.*, 105.
28. Pospisil, J. and Nespurek, S.(2000). *Prog. Polym. Sci.* **25**, 1261.
29. Pospisil, J. and Nespurek, S. (2005). *J. Optoelectron. Adv. Mater.* **7**, 1157.
30. Gerlock, J. L., Kucherov, A. V. and Smith, C. A. (2001). *Polym. Degrad. Stab.***73**, 201.
31. Banerjee, K. and Dureja, P. (1995). *Pestic. Sci.* **43**, 333.
32. Hussain, M., Persche, H. and Kutscher, R. (1990). *J. Pestic. Sci.*, **28**, 345.