Synthesis of Prostaglandins

by
CS. SZÁNTAY
and
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AKADÉMIAI KIADÓ, BUDAPEST

RECENT DEVELOPMENTS IN THE CHEMISTRY OF NATURAL CARBON COMPOUNDS

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PREFACE

Many share the opinion nowadays that the discovery of prostaglandins opened up a new chapter in human and veterinary medicine. Whether this optimism will be justified can only be revealed by the future since extensive clinical trials have only recently been started. It is promising that in some countries the use of prostaglandin $F_{2\alpha}$ in clinics has already been licensed for the termination of pregnancy during the second trimester. In 1974, I.C.I. started marketing its first prostanoid preparation "Equimate" for use in regulating the mating of horses.

In Hungary, Chemical and Pharmaceutical Works Chinoin had prostaglandin $F_{2\alpha}$ registered in 1975 under the proprietary name "Enzaprost" for the following main indications: (a) menstrual regulation, (b) termination of pregnancy, (c) dilatation of the human cervix prior to labour, or to induce abortion. Compared with mechanical dilatation the use of prostaglandin is a simple and safe clinical procedure.

This group of compounds belongs to the family of natural fatty acids and the members of the group are widely distributed in mammalian tissues. The concentration of prostaglandins is, however, extremely low, generally of the order of 1 μg/g and never exceeding the limit of 300 μg/g of undried tissue.

According to present-day concepts, prostaglandins control many a function of the human body, among others lipid metabolism, the activity of smooth muscles, the reproductive system, and they also affect the central nervous system. Prostaglandins are almost unrivalled in their activity judged on a weight basis: human smooth muscles respond to concentrations as low as 10^{-11} g/kg. Prostaglandins may well become useful in menstrual regulation, fertility control, contraception, and induction of labour; they may find application as hypotensives, antithrombotics, antiasthmatics, etc., and for the prolonged alleviation of obstruction of the nose in rhinitis. It has been reported that one of the prostaglandins has been used to regulate

gastric acid secretion in dogs and rats and that it acts as a preventive against the inducement of experimental ulcer in the rat.

Prostaglandin research has a history of more than forty years and dates back to 1930 when two New York gynaecologists, R. Kurzrok and C. C. Lieb reported the observations on human semen inducing contraction and relaxation of the human uterus. A few years later M. W. Goldblatt in England and U. S. von Euler in Sweden started their respective investigations on the lipid fractions isolated from human semen and on the vesicular gland of sheep. Von Euler coined the name prostaglandin for the active component. After the interruption caused by the war progress still remained rather slow because of lack of material to be investigated and the absence of suitable techniques for the separation and identification of the minute amounts that were available of these very sensitive substances.

Reinvestigation of the problem by S. Bergström at the Karolinska Institute in Stockholm from 1956 on with a team of experts in chromatography, ultramicroanalysis and mass spectroscopy, supported by the Upjohn Company, brought — after one year of intensive work the long due breakthrough with the prize of the isolation of the first crystalline prostaglandin.

The structural elucidation in 1962 of the first two members of the prostaglandin family was also accomplished at the Karolinska Institute, about three decades after the discovery of the biological activity.

Prostaglandin research gained momentum in 1964 when an *in vitro* method for the preparation of reasonable amounts of prostaglandins was developed concurrently in the United States, Sweden and the Netherlands, based on incubation of fatty acid precursors with an extract of sheep vesicular glands.

The first total syntheses of prostaglandins were achieved in 1968 by a team at the Upjohn Laboratories and a group led by E. J. Corey at Harvard University.

The availability of prostaglandins through biochemical and through total chemical synthesis stimulated extensive biological studies, including aspects related to human medicine. Scientific publications on prostaglandins began to appear from that time on at an ever increasing rate amounting now to about seven papers per day. A special journal devoted to the topic and entitled "Prostaglandins" was founded in 1972.

The competition in research on the synthesis, physiology and therapeutic applications of prostaglandins is exceptionally keen and overshadows even that on steroids in the postwar period. The most abundant, though still extremely meagre source of prostaglandins is the seminal fluid of man

and sheep. Minimal quantities are detectable in the uterus, lung, brain, eye, pancreas and kidney. It is generally believed that sooner or later it will be possible to trace prostaglandins in almost every tissue of mammals. Exceptionally, prostaglandins can be isolated from some lower organisms, e.g., as demonstrated by A. J. Weinheimer and R. L. Sproggins of Oklahoma University, from the Gorgonian *(Plexaura homomalla)*, a coral indigenous to the Caribbean.

Different kinds of prostaglandins exert different physiological effects both in the qualitative and in the quantitative sense. The number of natural prostaglandins known now exceeds twenty (for structure and nomenclature see Chapter 1). In the living organism they are formed by oxidation and successive cyclization of polyunsaturated fatty acids, called essential fatty acids. These have long been recognized as indispensable nutritional factors, their deficiency causing a special syndrome (including dermatosis, retarded growth, decreased fertility, increased loss of water through the skin) that can be eliminated by the administration of small amounts of polyunsaturated fatty acids. This phenomenon can now be partly explained by the role of the essential fatty acids as prostaglandin precursors.

This hypothesis has found support in the fact that it is possible to convert di-homo-γ-linoleic acid and arachidonic acid to prostaglandins by an enzyme preparation obtained from the vesicular gland of sheep.

Prostaglandins research threw new light on the mechanism of the action of certain long established drugs. For example, the anti-inflammatory effect of acetylsalicylic acid and its congeners has been interpreted by their action as prostaglandin antagonists.

Though it would be premature to draw final conclusions, many share the opinion that prostaglandins may achieve in therapy a place similar in importance to that held earlier by steroid hormones.

The potentials of prostaglandins stimulated Hungarian researchers at a quite early stage to join the world-wide race for their utilization. Two years after the accomplishment of the first total synthesis in 1968, research teams at the Institute of Organic Chemistry of the Technical University of Budapest and at Chemical and Pharmaceutical Works Chinoin undertook, as a joint venture, the development of an industrially viable process of synthesizing prostaglandins. The first few milligrams of the end product saw the light of day in 1972; pilot plant production started in 1974. Thus, preceded only by Upjohn in America and the Ono Company in Japan, Chinoin was the third to put prostaglandins on the market.

The extremely high physiological potency of natural prostaglandins is, however, associated with a very fast turnover of these substances. Prosta-

glandin E_2, which would be useful owing to its smooth muscle contracting effect for labour induction or for the termination of pregnancy, becomes up to 96% inactivated within 90 seconds of intravenous administration. Lack of organ- and tissue specificity presents further problems since, for example, prostaglandin E_2 induces the contraction not only of the smooth muscle of the uterus, but also those of the gastrointestinal tract thereby causing spasms and diarrhoea. The same compound is beneficial when inhaled as it dilates the bronchi and alleviates asthmatic fits, but as a side effect it leads to sore throat and coughing.

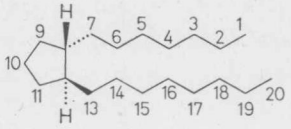
All this gives impetus for chemical research directed towards the synthesis of modified prostaglandins which, ideally, should combine high specificity with sufficiently slow degradation in the organism so as to permit their application as pharmaceuticals. The achievement of this end will require concentrated and tenacious efforts from organic chemists for many years to come. The very aim of this book is to further this work by reviewing the most important synthetic achievements in the prostaglandin field published up to the end of 1976, affording thus a guideline for the planning of strategy and tactics of further synthesis.

The authors gratefully acknowledge the help of Jenő Marosfalvi in his artful treatment of the figures and Béla Majoros in supplying the draft which aided in the writing of Section 3.7.

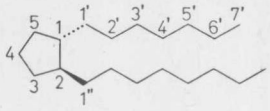
1. THE PROSTAGLANDINS

1.1 STRUCTURE AND NOMENCLATURE

Prostaglandins as defined by Bergström and co-workers in the early sixties can be derived from prostane, a hydrocarbon of twenty carbon atoms. Prostane (**1.1**) contains a cyclopentane ring in which the hydrogen atoms at the junction of the side chains are in *trans* relationship to each other [1–12].



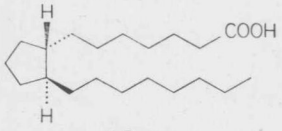
1.1



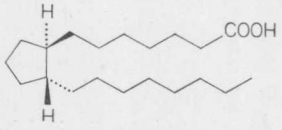
1.2

Because of the cumbersome nature of the nomenclature recommended by the IUPAC, that of Chemical Abstracts (C.A.) will be used [13]. Prostaglandins will be considered as derivatives of prostane or of the acid — prostanoic acid (**1.3**) — derived from it, and the numbering shown in formula **1.1** will be used. It should, however, be noted that certain authors apply another numbering system and denote prostaglandins as substituted cyclopentanes (**1.2**).

Prostanoic acid (**1.3**) contains two chiral carbon atoms (C_8 and C_{12}) of different constitution, thus the molecule can have four optical isomers of which two pairs are mirror images: prostanoic acid (**1.3**) and its mirror image, *ent*-prostanoic acid (**1.4**) are *threo* stereoismers, while isoprostanoic acid (**1.5**) and *ent*-isoprostanoic acid (**1.6**) represent the *erythro* forms.



1.3



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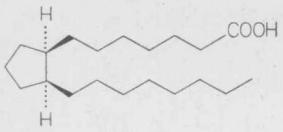
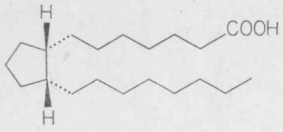


1.5



1.6

For the characterization of individual centres the descriptors α and β are used. The substituents of cyclopentane (as depicted in formulae **1.3–1.6**) may be below the plane of the ring, i.e. in the α configuration, or above this plane, i.e. in the β configuration.

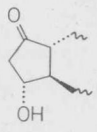
Consequently, the basic skeleton of prostaglandins (**1.3**) may be given the following names:

(a) prostanoic acid (according to C.A.); this is the name which will be used in this book;

(b) 1α-(6-carboxyhexyl)-2β-octylcyclopentane (conforming to the numbering of **1.2**);

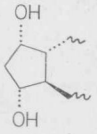
(c) 7-[(2β-octyl)cyclopentyl-1α]-heptanoic acid (according to IUPAC).

Depending on the substitution of the cyclopentane ring, there are six main types of prostaglandings (**1.7** to **1.12**). Type E (**1.7**) is characterized by the presence of a keto group in position 9 and an α-hydroxyl at C_{11}. In the F series (**1.8**) there are hydroxyl groups in both (9 and 11) positions.



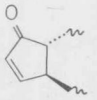
PGE

1.7



PGF

1.8



PGA

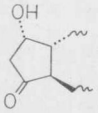
1.9

PGC

1.10

PGB

1.11



PGD

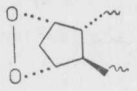
1.12

Types A (**1.9**), B (**1.11**) and C (**1.10**) contain a keto group in the 9-position and an endocyclic double bond. Compounds of the E and F series are also called primary prostaglandins. The designation A indicates that the compound can be prepared from type E by acid-catalyzed dehydration. In a similar way, B points to the elimination of water from type E by a base-

catalyzed reaction. Representatives of type A can be converted by base catalysis *via* C into the more stable B-type compounds.

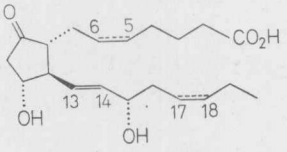
Later on, a natural D-type prostaglandin (**1.12**) was also isolated [14–16]. Members of this group of compounds contain a hydroxyl group at C_9 and a keto group in the 11-position.

Recently the range of natural prostaglandins has been extended by the isolation of endoperoxides (prostaglandins G and H), which are characterized by a peroxy function between C_9 and C_{11} (**1.13**). (*cf.* also Chapter 6.).



1.13

The number of double bonds in the side chains of prostaglandins varies from one to three and is indicated by a subscript numeral. All prostaglandins contain a double bond of a *trans*- or (*E*)-geometry in the hydroxyoctyl chain between C_{13} and C_{14} (e.g. **1.14**). Compounds with the subscript 2 possess an additional double bond of *cis*- or (*Z*)-geometry between C_5 and C_6. There is a third double bond also of (*Z*)-geometry between C_{17} and C_{18} in compounds with the subscript 3.



1.14

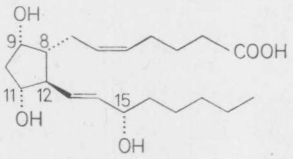
PGE_1: no double bond between C_5 and C_6, and C_{17} and C_{18}.
PGE_2: a double bond of (*Z*)-geometry between C_5 and C_6, no double bond between C_{17} and C_{18}.
PGE_3: double bonds of (*Z*)-geometry between C_5 and C_6, and C_{17} and C_{18}.

In 1968 IUPAC suggested the use of the letters *Z* (German, zusammen = together = *cis*) and *E* (German, entgegen = opposite = *trans*) [17, 18] for the description of the geometrical isomers instead of the earlier prefixes *cis* and *trans*. When classifying a compound, the sequence of substituents on the double bond is determined according to the sequence rule of Cahn, Ingold and Prelog, and when the two vicinal substituents of highest priority are on the same side (*cis*) the symbol *Z*, when they are on opposite sides (*trans*) the prefix *E* is used.

In F prostaglandins the letter α or β after the subscript numeral (or the term "*epi*") refers to the steric orientation of the C_9 hydroxyl group. A substituent is α-oriented if it is on the same side of the cyclopentane ring as the carboxyhexyl (C_1–C_8) side chain, and β-oriented (*epi*-compounds) if it

is opposite to this, i.e. *cis* to the hydroxyoctyl (C_{13}–C_{20}) side chain. In the other series of prostaglandins, the prefix "*epi*" designates configurational changes at C_{11} and C_{15}; the place is indicated in the name of the compound.

The absolute configuration of prostaglandins was determined by Nugteren and co-workers [19] in 1966. The hydroxyoctyl chain of prostaglandin E_1 was removed by oxidative ozonolysis, and the product was identified with the known (*S*)-2-hydroxyheptanoic acid. Since the relative configuration of natural prostaglandin $F_{1\alpha}$ was already known from Abrahamsson's earlier X-ray work [20], the absolute configuration of all of the centres of natural prostaglandins followed from the above configurational correlation.

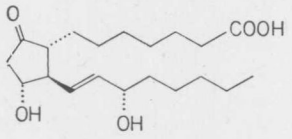


1.15

The absolute configuration of prostaglandin $F_{2\alpha}$ (**1.15**) is 8*R*, 9*S*, 11*R*, 12*R*, 15*S*. It should be noted that $2^5 = 32$ stereoisomers are possible due to the five chiral centres and 128 if allowing for the geometrical isomerism of the two double bonds.

Table 1.1

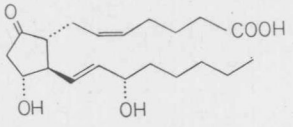
Structure and Nomenclature of Prostaglandins



PGE$_1$

1.16

11α,(15*S*)-dihydroxy-9-oxo-(13*E*)-prostenoic acid;
7-[3α-hydroxy-2β-(3α-hydroxy-(1*E*)-octenyl-5-oxo-cyclopentyl-1α]-heptanoic acid



PGE$_2$

1.17

11α,(15*S*)-dihydroxy-9-oxo-(5*Z*,13*E*)-prostadienoic acid;
7-[3α-hydroxy-2β-(3α-hydroxy-(1*E*)-octenyl)-5-oxocyclopentyl-1α]-(5*Z*)-heptenoic acid