Translated from *Uspekhi Khimii*, **46**, 1074 - 1096 (1977) U.D.C. 547.7.29.96

The Synthesis of Heterocyclic Analogues of Prostaglandins

E.I.Levkoeva and L.N.Yakhontov

The available information about the methods of synthesis of prostaglandin analogues containing the oxygen, sulphur, and nitrogen heteroatoms in the cyclic part of the molecule is described.
The bibliography includes 101 references.

CONTENTS

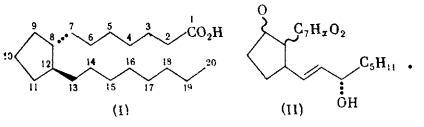
I. Introduction 565
II. Fundamental methods of synthesis of prostaglandins 565
III. Methods of synthesis of heterocyclic analogues of prostaglandins 567

I. INTRODUCTION

Prostaglandins (PG) are a comparatively recently discovered class of naturally occurring physiologically active substances which have been the subject of continuous attention by biologists and chemists in the last 10–15 years. Pharmacological studies have shown that prostaglandins exhibit an extremely broad spectrum of activity; their influence on the smooth musculature of various organs, their mediating role in the central and peripheral nervous systems in inflammatory processes, and their hormone-like and antihormonal activities have been investigated in detail[1,2].

The need for large amounts of prostaglandins, which are required in experimental and clinical research, led to the vigorous development of methods for the extraction and purification of prostaglandins and stimulated the search for methods of synthesis of prostaglandins and their analogues. Biological research on prostaglandins began in 1930,[3] but it was not until 1962 that the structures of the first three compounds of this series were established[4]. Approximately twenty natural prostaglandins have now been isolated.

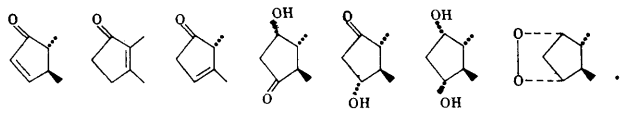
They are all derivatives of the hypothetical C_{20} prostanoic acid (I), the $C_{(8)} - C_{(12)}$ atoms of which are part of the cyclopentane ring:



(I) (II)

The $C_{(1)} - C_{(7)}$ side chain, terminating in a carboxy-group, is designated by convention as the α-chain and lies behind the plane of the cyclopentane ring. All prostaglandins have an oxygen-containing functional group attached to $C_{(9)}$ (OH or C=O), a hydroxy-group at $C_{(15)}$, and a *trans*-double bond (II) between $C_{(13)}$ and $C_{(14)}$.

Depending on the number and type of oxygen-containing functional groups, the degree of unsaturation of the cyclopentane ring, and the position of the double bond in the latter, prostaglandins are divided into groups designated by the letters A, B, C, D, E, F, G, and H:

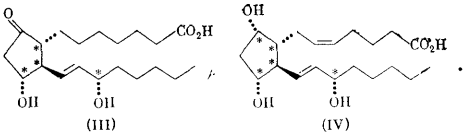


(A) (B) (C) (D) (E) (F_α) (G, H)

Natural prostaglandins may contain in the side chains, one, two, or three double bonds (apart from the obligatory 13,14-*trans*-bond, there may also be the 5,6-*cis*- and 17,18-*cis*-bonds). On the basis of the number of double bonds, each group is subdivided into series (for example PGE_1, PGE_2, and PGE_3). Natural PGF prostaglandins in which the hydroxy-group at $C_{(9)}$ is in the *cis*-position relative to the α-side chain have come to be designated as $PGF\alpha$, in contrast to the $PGF\beta$ compounds, epimeric with respect to $C_{(9)}$, which can only be obtained by synthesis.

II. FUNDAMENTAL METHODS OF SYNTHESIS OF PROSTAGLANDINS

The complete synthesis of natural prostaglandins presents considerable difficulties because of the complexity of their chemical structure rather than their lability. Thus the distinctive features of the PGE_1 (III) are as follows: 4 chiral centres, the β-oxo-group in the cyclopentane ring, the *trans*-disposition of all three ring substituents, and the presence of the acyclic hydroxy-group at $C_{(15)}$:



(III) (IV)

The complete synthesis of $PGF_2\alpha$ (IV) is further complicated by the presence of an additional chiral centre at $C_{(9)}$ and the necessity for the introduction of a second double bond. For this reason, the stereospecific syntheses of natural prostaglandins consist of many stages (up to 21 stages) and the yields of the final products are comparatively low.

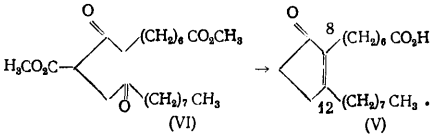
Analysis of the literature on the methods of synthesis of prostaglandins shows that all the methods can be divided into two groups:

1. Syntheses of prostaglandins based on long-chain compounds in which the cyclopentane ring is formed at one of the last stages of the synthesis.

2. Syntheses of prostaglandins based on cyclopentane derivatives.

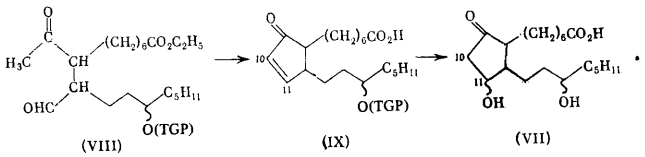
The synthetic methods of the first group can be conveniently regarded in their turn as a function of the C–C bond responsible for ring closure during the formation of the prostaglandin molecule. Thus one of the first attempts at the synthesis of prostaglandins was made in 1963 by

Samuelsson and Ställberg[5], who obtained 15-deoxy-13,14-dihydro-PGB_1 (V) by the intramolecular cyclisation of the diketone (VI) and the formation of the $C_{(8)} - C_{(12)}$ bond of the cyclopentane ring of PGB_1:



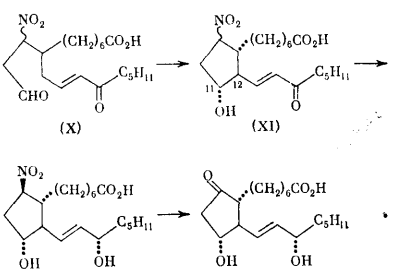
(VI) (V)

A stereoisomeric mixture of 13,14-dihydro-PGE_1 (VII) was obtained by Strike and Smith[6], who achieved during the synthesis the closure of the cyclopentane ring at the $C_{(10)} - C_{(11)}$ bond. For this purpose, they synthesised the aldehyde (VIII), which already contains both side chains of the prostaglandin molecule. The cyclisation of compound (VIII) led to the isolation of the enone (IX), which resulted in the formation of compound (VII) after epoxidation, hydrogenation, and the removal of the tetrahydropyranyl (TGP) protecting group:



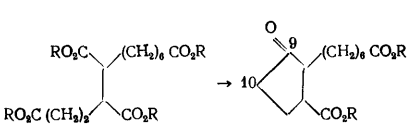
(VIII) (IX) (VII)

The methods for the formation of the $C_{(11)} - C_{(12)}$ bond in the prostaglandin molecule have been investigated in greatest detail. The study by Corey and coworkers[7,8] not only led to the preparation for the first time of pure crystalline prostaglandins, but also resulted in the development of methods which were subsequently used widely in prostaglandin chemistry; in particular, they employed the 9-nitrogroup as the precursor of the 9-oxo-group. The key compound in these syntheses was an aldehyde of type (X); it was subjected to aldol condensation to the enone (XI), which was shown to contain no 11-β-isomer whatsoever. Next, the 15-oxo-group was reduced with zinc tetrahydroborate, the nitro-group was transferred to the *trans*-position relative to the α-chain with the aid of bases, the $C_{(15)}$ epimers were separated chromatographically, and the nitro-group was converted into the oxo-group via the amino- and *N*-bromoamino-groups:

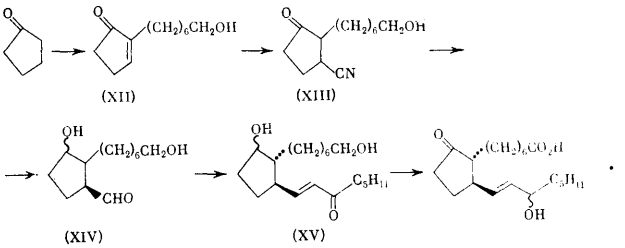


(X) (XI)

The closure of the cyclopentane ring at the $C_{(9)} - C_{(10)}$ bond by the Dieckmann reaction was achieved[9] in the course of the synthesis of (±)-11-deoxy-PGE_1:



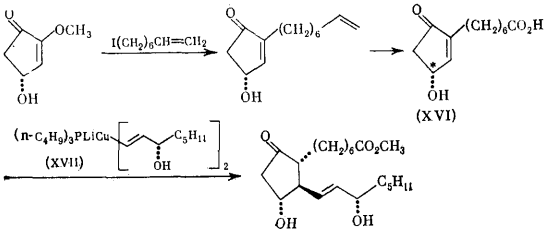
The second group of methods of synthesis of prostaglandins, from cyclopentane compounds, is based on both monocyclic and bicyclic systems containing the cyclopentane ring. An example of the synthesis achieved by the introduction of side chains into the molecule of a monocyclic cyclopentanone is provided by the scheme for the synthesis of 11-deoxy-PGE_1:[10]



(XII) (XIII) (XIV) (XV)

The enamine derived from cyclopentanone was alkylated by this method with ω-hydroxyoenanthaldehyde. The alkylation product was dehydrated to the enone (XII), whose reaction with acetone cyanohydrin led to the nitrile (XIII). The reduction of the latter with di-isobutylaluminium hydride (DIBAL) involved the oxo- and cyano-groups simultaneously. The resulting hydroxyaldehyde (XIV) was converted by the Wittig reaction into compound (XV), in which both hydroxy-groups were subsequently oxidised with chromium trioxide and the 15-oxo-group was selectively reduced with sodium tetrahydroborate.

The syntheses of prostanoids from monocyclic cyclopentane derivatives, which also proceed via intermediates such as the aldehyde (XIV) or enones of type (XVI), are nowadays used on a fairly wide scale. This can be explained, on the one hand, by the availability of the initial cyclopentane and, on the other hand, by the comparative simplicity of the subsequent modification to give the prostaglandin molecule. Thus the enone (XVI) contains only one chiral centre, the required α-chain is already present, and the stereospecific introduction of the second side chain can be successfully achieved[11] by means of the complex (XVII):



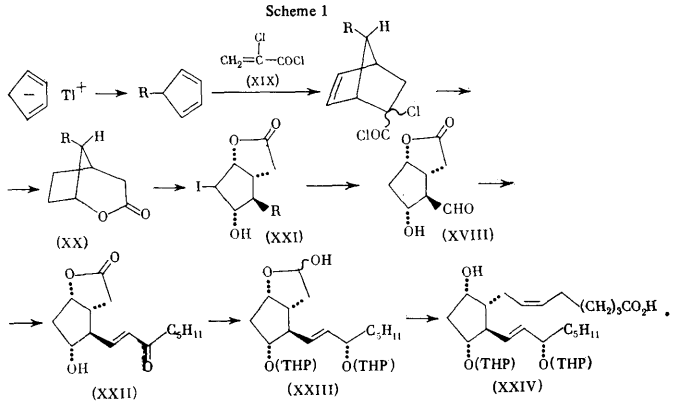
(XVI) (XVII)

Among the numerous methods for the synthesis of prostaglandins from bicyclic compounds, those developed by the Harvard group under the leadership of Corey, are of greatest interest. The key compound in these syntheses is the formyl-lactone (XVIII), which has come to be called in the literature the "Corey aldehyde". This compound is synthesised by Scheme 1[12,13] from pentadienylthallium. The product of the reaction of the latter with benzyl chloromethyl ether was then converted by condensation with the dienophile (XIX) into the corresponding bicyclic compound. The latter was converted by a series of reactions into 2-oxabicyclo[3,2,1] nonane, which formed the iodolactone (XXI) after hydrolysis and further reaction with potassium tri-iodide. This compound has the required configuration of all the nuclear centres. Its acylation, deiodination, and the conversion of the hydroxybenzyl group (R) into the formyl group led to the formyl-lactone (XVIII)—the "Corey aldehyde", which was subsequently made to undergo the Wittig condensation with the corresponding phosphorane to form compound (XXII). The 15-oxogroup in the latter was then reduced stereospecifically and the α-chain was

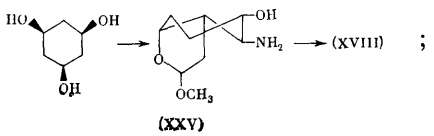
inserted (also by the Wittig reaction) after the conversion of the lactone into the lactol (**XXIII**).

Mild hydrolysis of the ether group led to the intermediate (**XXIV**) and then into $PGF_{2\alpha}$ after the removal of the THP protecting groups. Following the oxidation of the 9-hydroxy-group in compound (**XXIV**) and the removal of the THP protecting groups, PGE_2 was isolated. Compound (**XXIV**) was converted into a prostaglandin with a single double bond by hydrogenatoin over a palladium catalyst.

Scheme 1

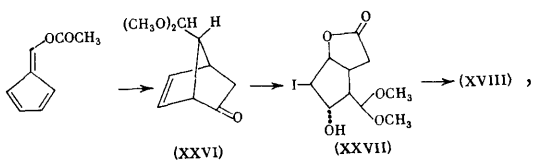


Corey's aldehyde (**XVIII**) became the key compound in various syntheses of prostaglandins. Several methods have been developed for its synthesis: from *cis*-cyclohexane-1,3,5-triol via the bicyclic aminoalcohol (**XXV**)[14]:

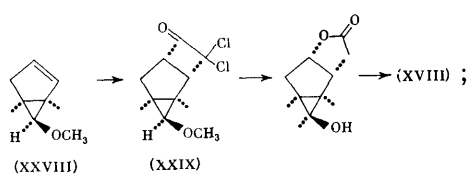


(**XXV**)

from acetoxyfulvene via bicyclo[2,2,1]heptene (**XXVI**) and the iodohydrin (**XXVII**):

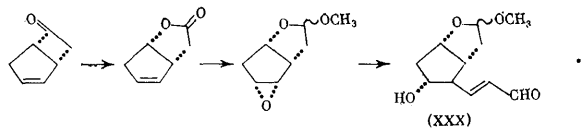


from the bicyclic ether (**XXVIII**) into which the elements of chloroketen are introduced stereospecifically with formation of the tricarbocyclic compound (**XXIX**)[16],



etc:

Another approach to the synthesis of prostaglandin structures involves the conversion of unsaturated bicyclic cyclopentanone derivatives into epoxides; the opening of the oxiran ring in the latter by specific reagents (for example[17], 1,3-bismethylthioallyl-lithium—the nucleophilic equivalent of the –CH=CH–CHO group) leads to an aldehyde of type (**XXX**):



A number of other novel methods for the synthesis of prostaglandins, which are outside the framework of the above schemes, have been described in special reviews, for example that of Mueller and Flanders[18].

III. METHODS OF SYNTHESIS OF HETEROCYCLIC ANALOGUES OF PROSTAGLANDINS

Research on methods of synthesis of prostaglandin analogues, which are easier to synthesise than natural prostaglandins but have the same or comparable biological activity, has developed on a wide scale in recent years.

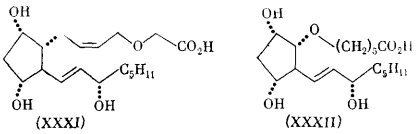
The search for synthetic analogues of prostaglandins is also dictated by other factors. In the study of the effect of prostaglandins on human organisms, undesirable side effects are frequently observed; a disadvantage of natural prostaglandins as medicinal substances is the short duration of their action, which necessitates their frequent administration. Furthermore, the wide variety of pharmacological effects creates major difficulties in their practical application. Preparations similar in structure to natural prostaglandins but acting more selectively on individual systems and functions of the organisms, are more stable, less toxic, and more easily administered to man than their natural prototypes are being sought for this reason. Finally, in many instances the structural analogues are synthesised in order to obtain prostaglandin antagonists and to elucidate the physiological role of natural prostaglandins.

A fairly large number of prostanoids, differing from natural prostaglandins by individual structural elements, have now been synthesised and their pharmacology investigated. In most instances, these are cyclopentane derivatives. They include active compounds with an alkyl chain longer than in prostaglandins[19] and prostanoids with shorter side chains[20] and with additional alkyl[21] or aryl[22] substituents. A wide variety of derivatives involving the functional groups of the prostaglandin molecule have been obtained, including oximes, thiosemicarbazides, semicarbazides[23], salts[24], and ethers[25]. Halogens[26,27] and heterocyclic residues[28,29] have been introduced into the side chain; the carboxy-group has been replaced by the sulpho-group[30], etc. The degree of unsaturation of the side chains[31,32] and the positions of the double bonds[33] have also been varied and oxo- and hydroxy-groups have been eliminated or additional ones have been introduced.

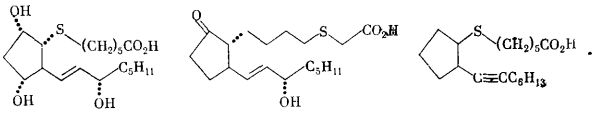
Such changes in the side chains led in most instances to a weakening of biological activity. On the other hand, many substances inhibiting the action of prostaglandins as well as a number of active preparations have been found.

The introduction of heteroatoms (sulphur or oxygen) into the α-chain led to the formation of a series of prostanoids exhibiting both prostaglandin-like and antagonistic activity. Prostanoids containing oxygen atoms in the 3-, 4-, and 5-positions[34] and in the 7-position[35,36] of the prostaglandin

molecule [compounds (XXXI) and (XXXII)] as well as 7-thiaprostaglandin (XXXIII)[37] and 3-thiaprostaglandin (XXXIV)[38] have been obtained in recent years:



(XXXI) (XXXII)

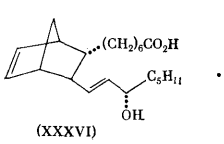


(XXXIII) (XXXIV) (XXXV)

The 7-thia-analogue (XXXV)[39], having a triple bond in the alkyl side chain and without an oxygen-containing functional group in the cyclopentane ring, showed a high activity in inhibiting PG-15-dehydrogenase. Analysis of compounds (XXXI)–(XXXIV) showed that a prostaglandin-like activity is shown only by the isomers in which all the chiral centres retain the absolute configuration characteristic of natural prostaglandins, while other isomers show little or no activity.

Various substituents, including halogen atoms[40,41] and alkoxy-[42], hydroxymethyl[44], alkyl[45], and other[46] groups, were introduced into the cyclic component of the prostaglandin molecule. The compounds synthesised, without an oxygen-containing functional group in the cyclopentane ring, for example[47], the 11-deoxy-analogue of PGE[32], 9-deoxyprostaglandin[48], etc. as well as prostaglandin analogues in which the cyclopentane ring was replaced by the benzene[49] or cyclohexane[50,51] rings, have also been synthesised.

Synthetic prostaglandin analogues having simpler structures in most cases did not show a distinctive effect on the smooth muscles in *in vitro* experiments, but interacted with the same receptors as prostaglandins, inhibiting their influence. Compound (XXXVI), which is a derivative of bicyclo[2,2,1]heptene, similar in structure to one of the postulated products of the biosynthesis of PGE_1, acts via a similar mechanism[52]. The authors[52] established that the compound inhibits selectively the isomerase responsible for the synthesis of PGE_1, but does not affect the reductase catalysing the formation of $PGF_{1\alpha}$.



(XXXVI)

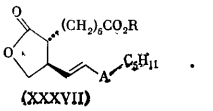
The introduction of a heteroatom into the cyclic part of the prostaglandin molecule was the next step in the modification of the structures of natural prostaglandins. The syntheses of heterocyclic prostanoids are based on the experience already gained with methods for the synthesis of natural prostaglandins. Both prostaglandins and their heteroanalogues are synthesised via two different schemes: either the side chains are attached to the complete cyclic fragment or ring closure is achieved in one of the last stages of the synthesis. The first pathway appears to have many advantages, since it makes it possible to vary the structures of the side chains and to attach them to a ring already containing the necessary stereochemical centres.

The syntheses of prostanoids containing oxygen, sulphur, and nitrogen atoms in the cyclic part of the molecule (oxa-, thia-, and aza-prostaglandins) have now been published.

1. Oxaprostaglandins

The majority of synthetic analogues of prostaglandins containing an oxygen atom in the cyclic part of the molecule are derivatives of tetrahydrofuran. In an attempt to obtain substances with potential antifertility activity, 9,10,11-mono-oxa- and 9,11-dioxa-prostaglandins were synthesised.

The first study on these lines involved the synthesis of 11-deoxy-10-oxaprostaglandin (XXXVII), carried out by Japanese workers in 1971[53]. The authors claimed that the compounds obtained exhibit a therapeutic activity similar to that of prostaglandins, and can be used in gastrointestinal disorders and in disturbances of blood pressure, as well as substances inducing natural birth and abortions.



(XXXVII)

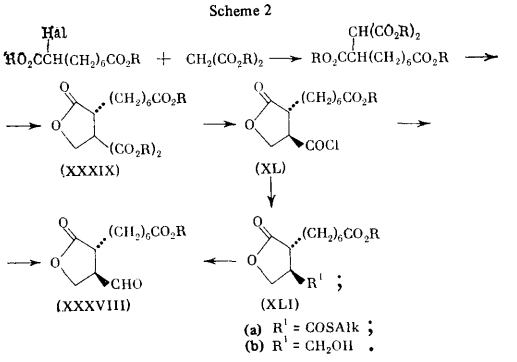
The key compound in the synthesis of a series of products (XXXVII) with R = H or alkyl and A = CO, CHOH, or CHOCOAlk is the aldehyde (XXXVIII), the synthesis of which is illustrated in Scheme 2.

The condensation of the diesters of α-halogenoazelaic and malonic acids in the presence of bases (alkali metal hydrides and alkoxides) led to the formation of the corresponding 8,9,9-tricarboxy-derivative of pelargonic acid, the condensation of which with formaldehyde led to the trisubstituted tetrahydrofuranone (XXXIX). The latter was then partly decarboxylated at 150–170° and converted into the acid chloride (XL) by reaction with thionyl chloride. Compound (XL) was further converted into the aldehyde (XXXVIII) in different ways: by direct hydrogenation in the presence of a palladium catalyst, or via the thioester (XLIa), which was then reduced to compound (XXXVIII) over a deactivated nickel catalyst, or by oxidising with dicyclohexylcarbodiimide (DCC) the alcohol (XLIb) obtained as a result of the dehydrogenation of compound (XLIa) over active Raney nickel.

The second alkyl chain was attached to the aldehyde (XXXVIII) using dimethyl 2-oxoheptylphosphonate and the 15-oxo-group was reduced with various alkali metal tetrahydroborates. The mixture of epimeric alcohols formed in this process was separated chromatographically and the ester group was hydrolysed in a weakly acid or weakly alkaline medium.

O-Acyl derivatives [(XXXVII), R = H, A = CHOCOalk] were also obtained by acylating the 15-hydroxy-group.

Scheme 2



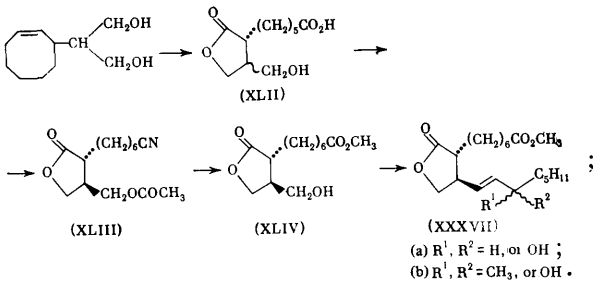
(XXXIX) (XL) (XXXVIII) (XLI)

(a) R^1 = COSAlk ;
(b) R^1 = CH_2OH .

An alternative synthesis of 10-oxaprostaglandins was published in 1974 (Scheme 3).[54] The initial tetrahydrofuranone (XLII), obtained by oxidising 2-(3-cyclo-octenyl)-propane-1,3-diol, already contained the α-chain, which was, however, shorter by one CH_2 group than in the prostaglandin. The α-chain was lengthened in the following way; after protecting the 11-hydroxymethyl group, the carboxy-group was reduced with diborane to an alcoholic group and was then converted via the tosylate into a nitrile group [compound (XLIII)]. After the alkaline hydrolysis of compound (XLIII) and esterification, the ester (XLIV) was isolated and its hydroxymethyl group was oxidised to the formyl group.

The further conversion into the 10-oxaprostaglandin (XXXVII) was achieved by a series of reactions which had already been thoroughly tested previously in syntheses of prostaglandins: the interaction of the aldehyde with dimethyl 2-oxoheptylphosphonate resulted in the introduction of the alkyl side chain, in which the 15-oxo-group was then reduced with sodium tetrahydroborate to the hydroxy-group:

Scheme 3

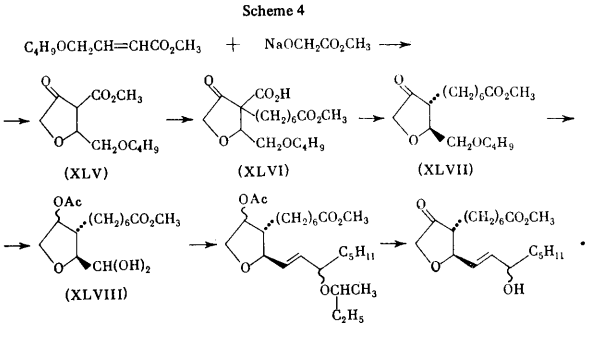


(XLII) (XLIII) (XLIV) (XXXVII)

(a) R^1, R^2 = H, or OH;
(b) R^1, R^2 = CH_3, or OH.

Fried and coworkers[55], who have been working for many years on the formation of prostanoids containing heteratoms in various parts of the molecule, achieved the synthesis of 11-oxaprostaglandin. The tetrahydrofuranone ring required to synthesise 11-oxaprostaglandin was formed by the condensation of 4-t-butoxybut-2-enoic acid with sodium methoxycarbonylmethoxide (Scheme 4). The resulting ketoester (XLV) was converted with alkali into the sodium salt, which was alkylated with methyl ω-iodo-oenanthate. Analysis of the ketoester (XLVII) obtained as a result of decarboxylation of compound (XLVI), showed that both side chains are in the required more stable *trans*-configuration:

Scheme 4



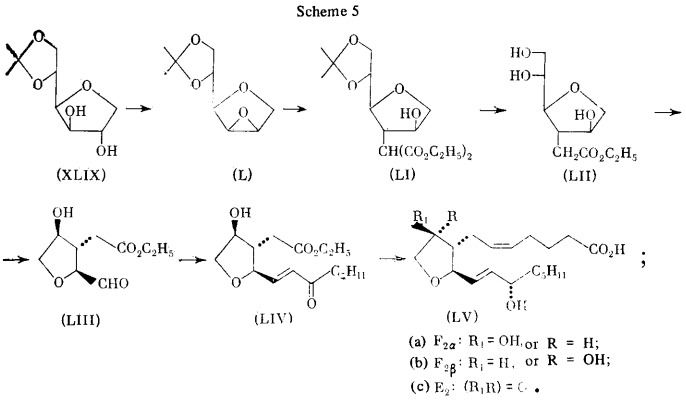
(XLV) (XLVI) (XLVII) (XLVIII)

The authors then reduced the t-butoxymethyl and 9-oxo-groups with zinc tetrahydroborate to alcoholic groups, selectively protected the 9-hydroxy-group, oxidised the 12-hydroxymethyl group with DCC to the aldehyde hydrate (XLVIII), and attached the alkyl chain via the Wittig reaction.

The 15-oxo-group was reduced with zinc tetrahydroborate; the resulting hydroxy-group was protected by ethyl vinyl ether, which permitted the oxidation of the 9-hydroxy-group to the carbonyl group with chromium trioxide after the removal of the 9-acetyl protecting group. The removal of the second protecting group in aqueous acetic acid led to a mixture of alcohols epimeric with respect to $C_{(15)}$, which were separated chromatographically. Both epimers exhibited a weak PGE-like activity in *in vitro* experiments (on the contraction of the smooth musculature of a section of the large intestine).

A novel stereospecific synthesis of 11-oxaprostaglandins containing a double bond in each side chain was developed by Canadian chemists[56] (Scheme 5). Starting with substituted 1,4-dihydrosorbitol (XLIX), the authors obtained via the monomethanesulphonate the epoxide (L), into which they subsequently introduced the malonic ester residue. After alkaline hydrolysis of compound (LI), partial decarboxylation, and esterification, the trisubstituted tetrahydrofuran (LII) was obtained, in which the ethylene glycol group was oxidised by sodium periodate to the formyl group. Treatment of the aldehyde (LIII) with dimethyl 2-oxoheptylphosphonate in the presence of sodium hydride gave an 80% yield of compound (LIV), which the authors regard as the key compound for the synthesis of 11-oxaprostanoids (LV):

Scheme 5



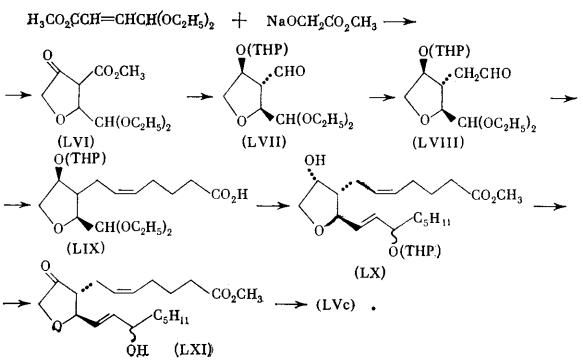
(XLIX) (L) (LI) (LII) (LIII) (LIV) (LV)

(a) $F_{2\alpha}$: R_1 = OH, or R = H;
(b) $F_{2\beta}$: R_1 = H, or R = OH;
(c) E_2: (R_1R) = O.

Vlattas and Lee[57] developed almost simultaneously with the Canadian workers[56] another version of the synthesis of the 11-oxa-analogue of PGE_2 [compound (LVc)] (Scheme 6). The disubstituted tetrahydrofuranone (LVI) was obtained by the condensation of methyl 4,4-diethoxycrotonate with sodium methoxycarbonylmethoxide. The reduction of compound (LVI) with sodium tetrahydroborate led to a mixture of epimeric alcohols. The main epimer was isolated chromatographically and, after protecting the hydroxy-group with THP, was converted into the aldehyde (LVII) by reaction with DIBAL. The following stage of the synthesis is of methodological interest: the formation of the homologous aldehyde (LVIII) via a vinyl sulphide. For this purpose, compound (LVII) was treated with triphenylphosphoranylidene(phenylthio)methane in dimethyl sulphoxide. The mixture of the *cis*- and *trans*-vinyl sulphides formed was converted by treatment with mercury acetate into an adduct, which was subjected to reductive cleavage with aluminium amalgam to the corresponding acetoxyphenylmercaptoacetal. Alkaline hydrolysis of the latter led to the aldehyde (LVIII), which was converted into compound (LIX) by reaction with sodium 5-triphenylphosphoranylidenepentanoate. The necessary alkyl chain was attached by the Wittig reaction with the corresponding phosphorane

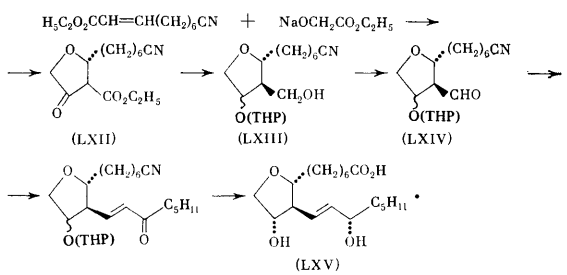
and the alcohol (LX) was converted into the ketone (LXI) by oxidation with thiocyanogen in dimethyl sulphide.

Scheme 6



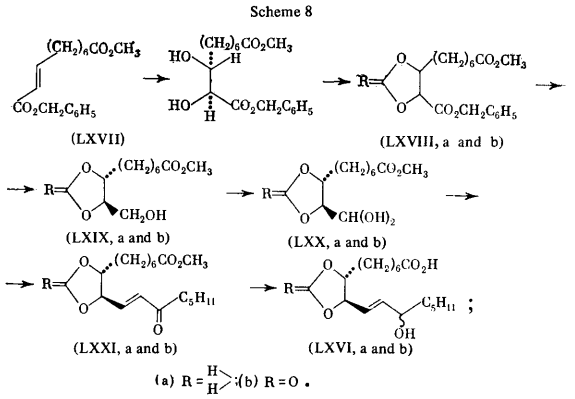
The synthesis of 9-oxaprostaglandin, published by Vlattas and Della Vecchia towards the end of 1974,[58] was achieved in accordance with one of the traditional schemes for the synthesis of PGE_1 and $PGF_{1\alpha}$ (see, for example, Caton[10]) (Scheme 7). The initial tetrahydrofuran derivative was obtained by condensing sodium ethoxycarbonylmethoxide with the corresponding substituted vinyl ether. The tetrahydrofuranone (LXII) synthesised already contained the required α-chain. The second chain was introduced into the ring after the reduction of the oxo- and ethoxycarbonyl group to alcoholic groups (in succession with sodium tetrahydroborate and lithium tetrahydroaluminate) and the conversion of the alcohol (LXIII) into the aldehyde (LXIV) under the influence of chromium trioxide by the Wittig reaction of compound (LXIV) with the corresponding phosphorane. After the reduction of the 15-oxo-group with sodium tetrahydroborate, the mixture epimeric with respect to $C_{(15)}$ was separated on a column of silica gel. The nitrile group was hydrolysed with potassium-hydroxide in the last stage of the synthesis of the 9-oxa-analogue of PGE_1 [compound (LXV)]:

Scheme 7



Scheme 8 describes the synthesis of prostanoids in the five-membered ring of which two hydroxymethine groups have been replaced by oxygen atoms. The authors[59] state that they undertook the synthesis of compounds of type (LXVI) after the interesting biological properties of prostaglandin analogues in the side chains of which the methylene groups have been replaced by heteroatoms [compounds (XXXII) and (XXXIII)[35,37]] became known.

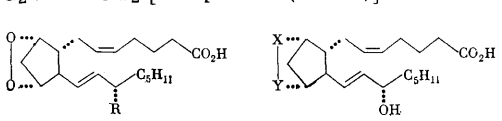
Scheme 8



Harrison et al. used as the initial compound the unsaturated *trans*-ester (XLVII), the synthesis of which they had developed previously for 9,11-bishydroxymethyl analogues of prostaglandins[44]. Hydroxylation of compound (LXVII) with osmium tetroxide in the presence of barium chlorate resulted in the formation of the corresponding diol, which was subsequently converted into the cyclic acetal (LXVIIIa) by heating with paraformaldehyde in benzene in the presence of perchloric acid. Hydrogenolysis of the benzyl group in compound (LXVIIIa) led to the corresponding acid which was converted into a mixed anhydride by a reaction with chlorocarbonic ester. The anhydride was reduced with sodium tetrahydroborate to the alcohol (LXIXa), whose oxidation with DCC led to the aldehyde hydrate (LXXa). The missing side chain was synthesised by the Wittig reaction and the 15-oxo-group was reduced with zinc tetrahydroborate. The mixture of epimers with respect to $C_{(15)}$ was separated chromatographically. The esters (LXXIa) were hydrolysed to the corresponding acids with a methanolic solution of sodium hydroxide.

In addition, the authors[59] developed the synthesis of a dioxaprostaglandin containing an oxo-group in the 10-position. In the synthesis of the heterocyclic nucleus, paraformaldehyde was replaced by phosgene, whose condensation with the diol was carried out in tetrahydrofuran in the presence of pyridine. The series of subsequent reactions, analogous to those employed in the synthesis of compound (LXVIa), led to compound (LXVIb). Both compounds exhibited a weak PGE_2 activity in *in vitro* experiments on their effect on the smooth muscles of a section of the large intestine.

Among the syntheses of oxaprostaglandins, mention must be made of the methods of synthesis of 2-oxabicyclo-[2,2,1]heptane analogues of the prostaglandin endoperoxides PGG_2 and PGH_2 [compounds (LXXII)]:

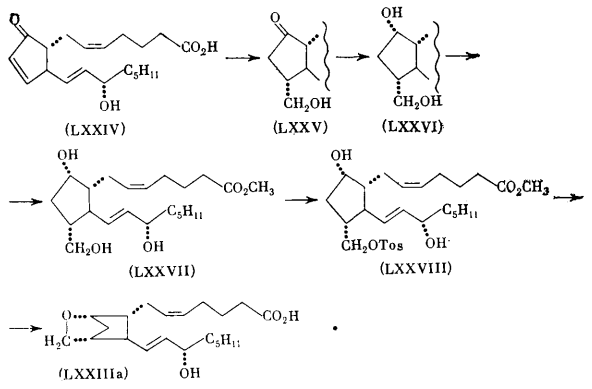


The compounds PGG_2 and PGH_2, which are intermediates in the biosynthesis of prostaglandins, have been obtained recently by biosynthesis; they were isolated and

characterised[60]. It was found that, despite their short half-life in an aqueous buffer, these compounds have an interesting spectrum of biological activity. This led Bundy[61] to synthesise the prostaglandin analogues (LXXIII) by replacing one of the peroxide oxygen atoms in the PGH_2 molecule by the methylene group.

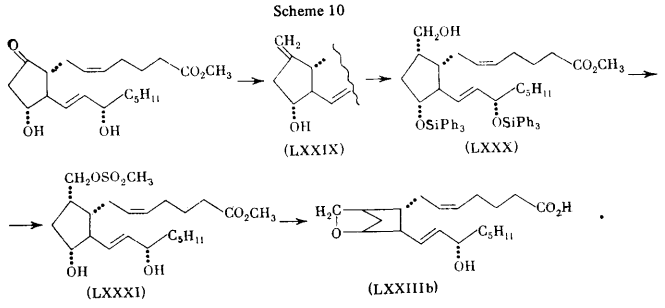
The 11-hydroxymethyl group was introduced (Scheme 9) into the carbon skeleton of PGA_2 [compound (LXXIV)], obtained from the coral *Plexaura Homomalla*, by irradiating a methanol solution of PGA_2 in the presence of benzoquinone. The resulting mixture of epimeric alcohols (LXXV), with the 11-α-isomer predominating, was separated chromatographically. The oxo-group in the ring of the 11-α-isomer isolated was reduced with lithium perhydro-9b-boraphenalyl hydride and the reaction was so stereospecific that the yield of the required 9-α-isomer (LXXVI) reached 94%. After the esterification of the dihydroxy-acid (LXXVI) with diazomethane, the primary alcoholic group in compound (LXXVII) was selectively converted into the toluene-*p*-sulphonate ester (LXXVIII). Subsequent treatment of compound (LXXVIII) with potassium hydroxide in an aqueous methanol solution at room temperature made it possible to achieve both intramolecular substitution and hydrolysis of the ester group.

Scheme 9



The synthesis of compound (LXXIIIb), in which the oxygen atom attached to $C_{(9)}$ in the PGH_2 molecule has been replaced by a methylene group, is illustrated in Scheme 10.

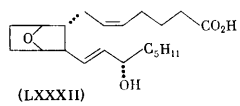
Scheme 10



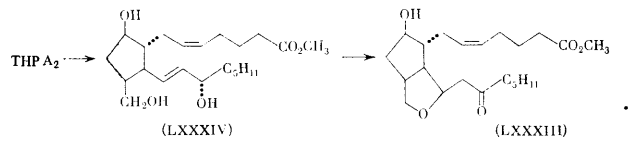
The methylene group was introduced in the 9-position of the methyl ester of PGE_2 by treating the latter with *N*-methylphenylimidoylmethylmagnesium chloride in tetrahydrofuran and subsequent reductive cleavage of the resulting adduct with aluminium amalgam. The yield of the 9-methylene derivative (LXXIX) was 75%.

The subsequent stages of the synthesis—the protection of the 11- and 15-hydroxy-groups with triphenylsilyl groups and selective hydroboration of the 9-methylene group with 9-borabicyclo[3,3,1]nonane (9-BBH)—led to the corresponding primary alcohol (LXXX). The stereochemistry of compound (LXXX) was determined by the preferred attack by 9-BBH from the less shielded side of the molecule and was confirmed by the ease of the subsequent cyclisation involving the 11-α-hydroxy-group. For this purpose, the methanesulphonate was obtained initially by reaction with the primary alcoholic group, the silyl protecting group was removed, and the resulting monomethanesulphonate (LXXXI) was treated with an aqueous methanol solution of potassium hydroxide. Like PGH_2, the cyclic ethers (LXXXIII, a and b) manifested a broncho-constricting activity in experiments on animals.

A report[62] of the synthesis of another series of endoperoxide analogues—derivatives of 7-oxabicyclo[2,2,1]-heptane (LXXXII)—was published recently. These compounds were obtained by the condensation of triethylphosphonosorbic acid esters and dimethyl 2-oxoheptylphosphonate with the corresponding derivatives of 7-oxabicyclo[2,2,1]heptane:

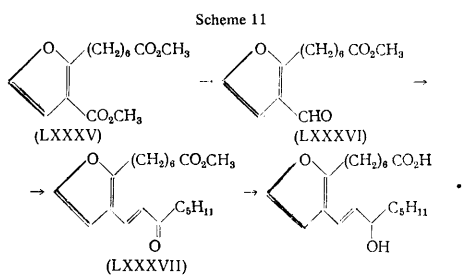


Yet another derivative of tetrahydrofuran, whose structure is similar to that of PGE_2, was obtained in the course of the synthesis of 9,11-bishydroxymethyl analogues of PGE_2.[63] Compound (LXXXIII) is formed when the triol (LXXXIV) is oxidised with 2,3-dichloro-5,6-dicyanobenzoquinone, which results in the conjugate addition of the *cis*-hydroxymethyl group to the intermediate enone:



The synthesis of oxygen-containing heteroaromatic prostanoids derived from furan and oxazole has also been described[64]. Scheme 11 was put forward for the synthesis of a furan analogue of prostaglandin. Dimethyl 3-oxosebacate was treated with chloroacetaldehyde; the resulting methyl 2-(6-methoxycarbonylhexyl)furan-3-carboxylate (LXXXV) was converted into the aldehyde (LXXXVI). The Wittig reaction of the latter with the corresponding phosphorane led to methyl 15-oxo-9-oxaprosta-8(12), 10,13-*trans*-trienoate (LXXXVII), in which the 15-oxo-group was then reduced and the ester group was hydrolysed:

Scheme 11



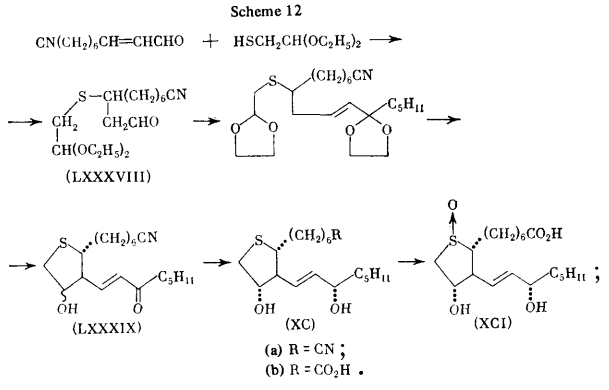
2-, 9-, and 11-Thiaprostaglandins

Literature data are available about the synthetic analogues of prostaglandins containing a sulphur atom in the 9- or 11-position in the molecule. They are all tetrahydrothiophen derivatives.

The synthetic scheme selected by Vlattas and Della-Vecchia[65] to obtain 9-thiaprostaglandins and their $C_{(11)}$ and $C_{(15)}$ epimers is fairly well known and is frequently used to synthesise natural prostaglandins (see, for example, Corey et al.[66]). A characteristic feature of the scheme is the closure of the cyclic components of the molecule (with formation of the $C_{(11)} - C_{(12)}$ bond) after both side chains have been synthesised (Scheme 12).

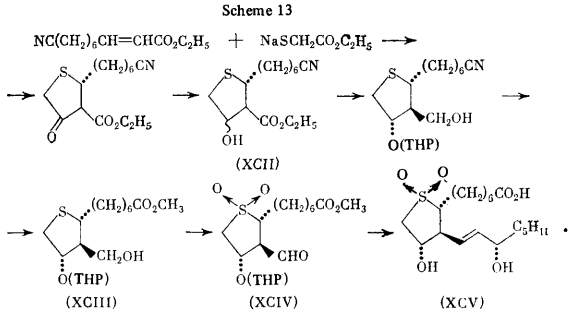
The condensation of 9-cyanononenal with the diethyl acetal of mercaptoacetaldehyde led to the adduct (**LXXXVIII**) which reacted under the conditions of the Wittig reaction with 1-tributylphosphoranylidene-2-heptanone to form the corresponding enone. After protecting both oxo-groups with ethylene glycol and subsequent intramolecular cyclisation of the dieketal (in the presence of toluene-*p*-sulphonic acid), a mixture of epimers of compound (**LXXXIX**) with respect to $C_{(11)}$ was obtained. Chromatographic separation of the isomers and subsequent reduction of the 15-oxo-group in the more polar isomer with zinc tetrahydroborate led to the formation of a new epimeric mixture with respect to $C_{(15)}$, from which the more polar isomer (**XCa**) was isolated on a column with silica gel. The isomer was then hydrolysed in an aqueous methanol solution of potassium hydroxide to (±)-9-thiaprostaglandin (**XCb**). In addition, a mixture of the isomeric sulphoxides (**XCI**) was obtained by oxidising compound (**XCb**) with sodium peroxide.

Scheme 12



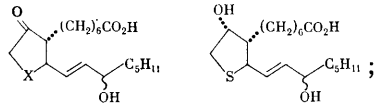
The same workers developed simultaneously an alternative scheme for the synthesis of 9-thiaprostaglandins[67] (Scheme 13). The tetrahydrothiophen ring was formed at the beginning of the synthesis. For this purpose, ethyl 9-cyanonon-2-enoate was condensed with the sodio-derivative of thioglycolic ester. The resulting substituted tetrahydrothiophenone was then reduced with sodium tetrahydroborate to a mixture of epimeric products (**XCII**) with respect to $C_{(11)}$, which was separated chromatographically. After protecting the 11-hydroxy-group in the more polar isomer (**XCII**) with THP, the ester group was reduced and the resulting hydroxynitrile was then converted into the corresponding hydroxyester (**XCIII**) by alkaline hydrolysis in methanol and esterification with diazomethane:

Scheme 13



The sulphide (**XCIII**) was then oxidised with *m*-chloroperbenzoic acid to a sulphone, which was in its turn converted into the aldehyde (**XCIV**) by treatment with chromium trioxide. Compound (**XCIV**) was converted into (±)-9-thia-PGE_1 dioxide (**XCV**) with the aid of reactions usually employed in this series of conversions: the introduction of the alkyl chain by the Wittig reaction, the reduction of the 15-oxo-group by sodium tetrahydroborate followed by the chromatographic separation of the epimeric alcohols, and the hydrolysis of the ester group in the 11-position with potassium carbonate in methanol. The enantiomeric form of compound (**XCV**) was obtained by esterifying the 11-hydroxy-group of *R*(-)-α-methoxyphenylacetyl chloride at the enone stage.

Derivatives of 11-thiaprostaglandin in which the sulphur atom replaces the hydroxymethine group in the 11-position of the PGE_1 [compounds (**XCVI**, a and b)] and $PGF_{1\alpha}$ [compound (**XCVII**)] molecules, have been recently synthesised in accordance with Scheme 14:[68]

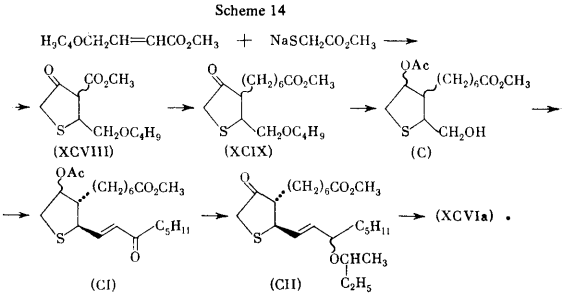


In this case the tetrahydrothiophen ring was formed from methyl 4-t-butoxybut-2-enoate and the sodio-derivative of thioglycolic ester. The resulting tetrahydrothiophenone (**XCVIII**) was alkylated with methyl 7-iodo-oenanthate and then the methoxycarbonyl group was eliminated by treatment with lithium hydride in boiling dimethylformamide. The 9-oxo-group in the resulting ketoester (**XCIX**) was reduced with sodium tetrahydroborate and the resulting hydroxy-group was protected by treatment with acetic anhydride, while the t-butyl group was eliminated by treatment with a mixture of 48% aqueous hydrofluoric acid and tetrahydrofuran.

The alcohol (C), isolated in this reaction, was subsequently converted into the corresponding aldehyde hydrate (as in Scheme 4) and then into the enone (**CI**). Analysis of the structure of compound (**CI**) enabled the authors to claim that the side chains in the compounds obtained are in the most stable *trans*-configuration. Next, compound (**CI**) was converted by treatment with zinc tetrahydroborate into a mixture of alcohols epimeric with respect to $C_{(15)}$ and the 15-hydroxy-group was protected with ethyl vinyl ether, after which the 9-hydroxy-group was oxidised with DCC in

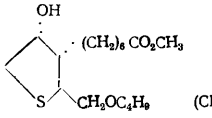
dimethyl sulphoxide to form the ketone (CII). Mild hydrolysis of the ester groups then led to the isolation of 15(α + β)-hydroxy-9-oxo-11-thiaprost-13-enoic acid (XCVIa):

Scheme 14



In order to obtain the sulphoxide (XCVIb), the ketone (CII) was oxidised with *m*-chloroperbenzoic acid, which led to the formation of a mixture of the isomeric methyl esters of the sulphoxide.

Compound (XCVII), the thia-analogue of $PGF_1\alpha$, was synthesised by reducing the ketone (XCIX) with potassium tri-(s-butyl)hydroborate to the 8,9-*cis*-alcohol (CIII):



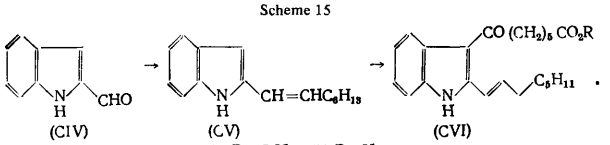
Using the methods described above, compound (CIII) was converted into the corresponding acetoxyalcohol and then into the aldehyde, the enone, and a mixture of alcohols epimeric with respect to $C_{(15)}$. Further hydrolysis yielded 9α, 15(α + β)-dihydroxy-11-thiaprost-13-enoic acid (XCVIII). 11-Thiaprostaglandins showed a weak PGE_2-like activity on the smooth muscles of a section of the large intestine in *in vitro* experiments.

3. Azaprostaglandins

The prostaglandin analogues in which the cyclopentane ring has been replaced by a nitrogen-containing heterocycle synthesised hitherto are indole, pyrrolidine, pyrazolidine, oxazole, and thiazole derivatives.

2-Oct-1-enylindole (CV) was obtained from indole-2-aldehyde (CIV) and heptylidenephosphorane[69,70] (Scheme 15). The authors selected the chloride of the half-ester of pimelic acid in order to introduce the side chain with a carboxy-group, simulating the α-chain of prostaglandin molecules. Acylation of the organomagnesium derivative (CV) with this reagent took place with a high yield (80%) and led to ethyl 7-[2-(oct-1-enyl)-3-indolyl]-7-oxoheptanoate (CVIa) (the ratio of the *cis*- and *trans*-isomers was 45 : 55):

Scheme 15

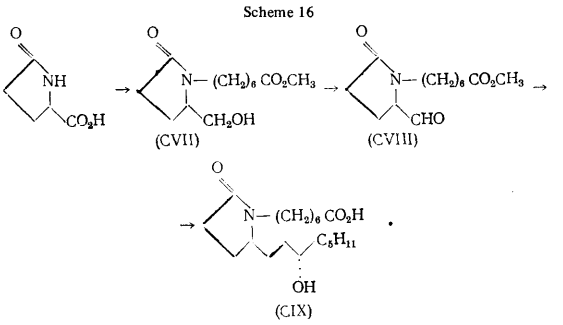


(a) R=C_2H_5; (b) R=H.

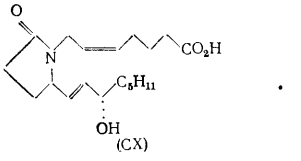
Alkaline hydrolysis of compound (CVIa) gave the *trans*-isomer of the corresponding acid (CVIb), whose structure was confirmed by ^1H NMR.

The authors based the syntheses of (±)-11-deoxy-8-aza-prostaglandins, the pyrrolidine analogues of PGE_1 and PGE_2,[71,72] also on the "complete" cyclic component of the molecule (Scheme 16). 5-Hydroxymethyl-1-(6-methoxycarbonylhexyl)pyrrolidin-2-one (CVII) was obtained from the readily available (±)-pyroglutamic acid (five stages):

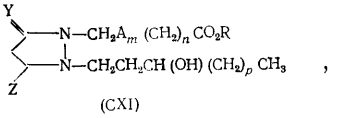
Scheme 16



The subsequent formation of the side chain, involving the oxidation of the alcoholic group to the aldehyde group, the condensation of the aldehyde (CVIII) with dimethyl 2-oxoheptylphosphonate, and the reduction of the resulting enone, presented no difficulties according to the authors' report and led to a mixture of alcohols epimeric with respect to the $C_{(15)}$ and separated chromatographically. The 8-aza-analogue of PGE_2 [compound (CX)] was also synthesised on the basis of a suitably modified scheme[71]:



A series of diazaprostaglandins—derivatives of pyrazolidine having the general formula (CXI)—have been synthesised by Scribner[73] in order to obtain prostaglandin inhibitors (Scheme 17):

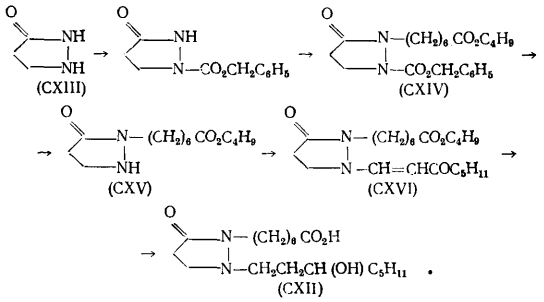


where A = CH = CH or C≡C, R = H, metal, amine salt, alkyl, or halogenoalkyl, m = 0 or 1, n = 0–6, p = 0–6, and Y, Z = O or H_2.

According to the author[73], certain compounds of this class can be used as antipyretic, analgesic, and anti-inflammatory agents, and also in the treatment of certain forms of diarrhoea and shock. The synthesis of prostanoids of type (CXI) is facilitated relative to that of natural prostaglandin by the fact that compound (CXI) contains not more than one asymmetric carbon atom (in the side chain) and the asymmetric ring carbon atoms have been replaced by nitrogen atoms. As an example, Scheme 17 presents

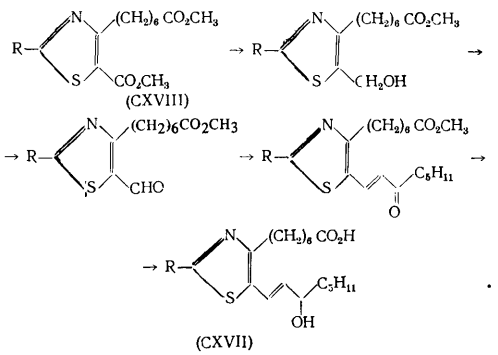
the synthesis of one representative of this series, namely (±)-15-hydroxy-9-oxo-8,12-diazaprostanoic acid (**CXII**):

Scheme 17



The more basic nitrogen atom was first protected in the initial pyrazolidinone (**CXIII**) with the aid of benzyl chloroformate, after which the compound was alkylated at the second nitrogen atom with t-butyl 7-bromo-oenanthate to form the ester (**CXIV**). Hydrogenation of compound (**CXIV**) over palladium made it possible to remove the protecting group from the basic nitrogen atom in the pyrazolidinone ring, after which the product (**CXV**) was converted by refluxing with oct-1-yn-3-one in alcohol into the enaminoketone (**CXVI**), which was subsequently reduced, without prior purification, with hydrogen in the presence of a platinum catalyst (the $C_{(13)} - C_{(14)}$ bond) and with sodium tetrahydroborate (the 15-oxo-group). The mixture of alcohols epimeric with respect to $C_{(15)}$ was separated chromatographically. It is noteworthy that 8,12-diazaprostanoids (**CXII**) are the first example of synthetic basic analogues of prostaglandins.

Prostanoids containing nitrogen and sulphur atoms in the cyclic part of the molecule have been synthesised by Hungarian chemists[64]. In the synthesis of thiazole analogues of prostaglandins [compound (**CXVII**)], the heterocyclic ring is formed as a result of the condensation of dimethyl 2-chloro-3-oxosebacate with various thioamides. The resulting methyl 4-(6-methoxycarbonylhexyl)thiazole-5-carboxylate (**CXVIII**) was converted into compound (**CXVII**) in accordance with the scheme



Like the furan and oxazole analogues of prostaglandins (see Section III, subsection 2), the thiazole analogue (**CXVII**) inhibits enzymes which catalyse the further conversion of prostaglandins (15-hydroxy-PG-dehydrogenase and PGA-isomerase) and exhibits a prostaglandin-like effect in certain biological tests.

After the preparation of the article for publication, a number of communications on the subject of the review were published[74-101].

REFERENCES

1. M.D.Mashkovskii, Farmakol.i Toksikol., 37, 109 (1974).
2. K.Khommel, W.Fischer, and S.Shlimovich, Sov. Meditsina, No.11, 77 (1973).
3. R.Kurzrok and C.C.Lieb, Proc.Soc.Exp.Biol., 28, 268 (1930).
4. S.Bergström, R.Ryhage, B.Samuelsson, and J.Sjövall, Acta Chem.Scand., 16, 501 (1962).
5. B.Samuelsson and G.Ställberg, Acta Chem.Scand., 17, 810 (1963).
6. D.P.Strike and H.Smith, Tetrahedron Letters, 4393 (1970).
7. E.J.Corey, N.H.Andersen, R.M.Carlson, J.Paust, E.Vedejs, I.Vlattas, and R.E.K.Winter, J.Amer.Chem.Soc., 90, 3245 (1968).
8. E.J.Corey, I.Vlattas, and K.Harding, J.Amer. Chem.Soc., 91, 535 (1969).
9. N.Finch, L.DellaVecchia, J.J.Fitt, R.Stephani, and I.Vlattas, J.Org.Chem., 38, 4412 (1973).
10. M.P.L.Caton, Tetrahedron Letters, 773 (1973).
11. C.J.Sih, R.G.Salmon, P.Price, R.Sood, and G.Peruzzotti, J.Amer.Chem.Soc., 97, 857 (1975).
12. E.J.Corey, U.Koelliker, and J.Neuffer, J.Amer. Chem.Soc., 93, 1489 (1971).
13. E.J.Corey, S.M.Albonico, U.Koelliker, T.K.Schaaf, and R.K.Varma, J.Amer.Chem.Soc., 93, 1491 (1971).
14. R.B.Woodward, J.Gosteli, I.Ernst, R.J.Friary, G.Nestler, H.Raman, R.Sitren, C.Suter, and J.K.Whitesell, J.Amer.Chem.Soc., 95, 6853 (1973).
15. E.D.Brown, R.Clarkson, I.J.Leeney, and G.E.Robinson, Chem.Comm., 642 (1974).
16. E.J.Corey, Z.Arnold, and J.Hutton, Tetrahedron Letters, 307 (1970).
17. E.J.Corey and R.Noyori, Tetrahedron Letters, 311 (1970).
18. R.A.Mueller and L.E.Flanders, Ann.Repts Med. Chem., 9, 162 (1974).
19. A.P.Labhsetwar, Nature, 238, 400 (1972).
20. H.C.Arndt and W.G.Biddlecom, Prostaglandins, 7, 387 (1974).
21. W.Lippmann, Prostaglandins, 7, 231 (1974).
22. D.Binder and J.Bowler, Prostaglandins, 6, 87 (1974).
23. US.P. 3 723 528 (1973).
24. US.P. 3 725 469 (1973).
25. G.A.Youngdale and F.H.Linkoln, Prostaglandins, 6, 207 (1974).
26. BRD Appl. 2 320 368 (1973); Chem.Abs., 80, 36746 (1974).
27. US.P. 3 767 695 (1973).

28. US.P. 3 853 854 (1974); Chem. Abs., **82**, 86271 (1975).
29. BRD Appl. 2 348 632 (1974); Chem. Abs., **81**, 37323 (1974).
30. Y. Iguchi, S. Kori, and M. Hayashi, J. Org. Chem., **40**, 521 (1975).
31. J. Fried and C. H. Lin, J. Medicin. Pharmaceut. Chem., **16**, 429 (1973).
32. J. F. Bagli, T. Bogri, and S. N. Sehgal, Tetrahedron Letters, 3329 (1973).
33. H. Wakatsuka, S. Kori, and M. Hayashi, Prostaglandins, **8**, 341 (1974).
34. N. A. Nelson, R. W. Jackson, and W. L. Miller, "International Conference on Prostaglandins, Florence, Italy, 1975", p. 72.
35. J. Fried, M. M. Mehra, and W. L. Kao, J. Amer. Chem. Soc., **93**, 5594 (1971).
36. J. Fried, M. M. Mehra, and W. L. Kao, Tetrahedron Letters, 2695 (1970).
37. J. Fried, M. M. Mehra, and Y. Y. Can, J. Amer. Chem. Soc., **96**, 2759 (1974).
38. K. F. Bernardy, J. F. Polletto, and M. J. Weiss, Tetrahedron Letters, 765 (1975).
39. J. Fried, M. M. Mehra, and Y. Y. Can, J. Amer. Chem. Soc., **96**, 6759 (1974).
40. US.P. 3 755 426 (1973).
41. BRD Appl. 2 344 740 (1974); Chem. Abs., **81**, 25191 (1974).
42. French P. 2 162 212 (1973); Chem. Abs., **80**, 82218 (1974).
43. Japanese P. 7 431 647 (1974); Chem. Abs., **81**, 25183 (1974).
44. I. T. Harrison, R. Grayshan, T. Williams, A. Semenovski, and J. H. Fried, Tetrahedron Letters, 5151 (1972).
45. A. Guzman and P. Crabbé, Chem. Ind. (London), 635 (1973).
46. A. Guzman, M. Vera, and P. Crabbé, Prostaglandins, **8**, 85 (1974).
47. Japanese P. 7 426 259 (1974); Chem. Abs., **81**, 25181 (1974).
48. N. Finch, J. J. Fitt, and J. H. S. Hsu, J. Org. Chem., **40**, 206 (1975).
49. A. Collet and J. Jacques, Chem. Theraphie, **5**, 163 (1970).
50. J. Fried, T. S. Santhanakrishnan, J. Himizu, C. H. Lin, S. H. Ford, B. Rubin, and E. O. Grigas, Nature, **223**, 208 (1969).
51. N. S. Crossley, Tetrahedron Letters, 3327 (1971).
52. P. Wlodawer, B. Samuelsson, S. M. Albonico, and E. J. Corey, J. Amer. Chem. Soc., **93**, 2815 (1972).
53. J. U. S. Himizu, S. K. K. Harigaya, A. A. Ichida, K. O. S. Yoshikawa, and M. C. Sato, BRD Appl. 2 229 225 (1972); Chem. Abs., **78**, 111102 (1973).
54. F. M. Hauser and R. C. Huffman, Tetrahedron Letters, 905 (1974).
55. I. T. Harrison, V. R. Fletcher, and J. H. Fried, Tetrahedron Letters, 2733 (1974).
56. S. Hanessian, P. Dextraze, A. Fougerousse, and I. Guindon, Tetrahedron Letters, 3983 (1974).
57. I. Vlattas and V. O. Lee, Tetrahedron Letters, 4451 (1974).
58. I. Vlattas and L. DellaVecchia, Tetrahedron Letters, 4455 (1974).
59. I. T. Harrison and V. R. Fletcher, Tetrahedron Letters, 2729 (1974).
60. M. Hamberg, Proc. Nat. Acad. Sci. U.S.A., **71**, 345 (1974).
61. G. L. Bundy, Tetrahedron Letters, 1957 (1975).
62. T. A. Eggelte, H. de Koning, and H. O. Huisman, "International Conference on Prostaglandins, Florence, Italy, 1975", p. 68.
63. A. Guzman and J. M. Muchowski, Tetrahedron Letters, 2053 (1975).
64. G. Ambrus and I. Barta, "International Conference on Prostaglandins, Florence, Italy, 1975", p. 66.
65. I. Vlattas and L. DellaVecchia, Tetrahedron Letters, 4459 (1975).
66. E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, J. Amer. Chem. Soc., 90, 3247 (1968).
67. I. Vlattas and L. DellaVecchia, Tetrahedron Letters, 4267 (1974).
68. I. T. Harrison, R. J. K. Taylor, and J. H. Fried, Tetrahedron Letters, 1165 (1975).
69. V. G. Avramenko, N. N. Levinova, V. D. Nazina, and N. N. Suvorov, Khim. Geterotsikl. Soed., 204 (1975).
70. V. G. Avramenko, Doctoral Thesis, Mendeleev Moscow Institute of Chemical Engineering, Moscow, 1974.
71. H. de Koning and H. O. Huisman, "Vth Symposium on the Chemistry of Heterocyclic Compounds, Bratislava, 1975", p. 102.
72. G. Bolliger and J. M. Muchowski, Tetrahedron Letters, 2931 (1975).
73. R. M. Scribner, BRD Appl. 2 322 193 (1973); Chem. Abs., 80, 986 (1974).
74. G. J. Lourens and J. M. Koekemoer, Tetrahedron Letters, 3719 (1975).
75. G. J. Lourens and J. M. Koekemoer, Tetrahedron Letters, 3715 (1975).
76. J. W. Bruin, H. de Koning, and H. O. Huisman, Tetrahedron Letters, 4599 (1975).
77. E. J. Corey, K. C. Nikolaou, Y. Machida, C. L. Malsten, and B. Samuelsson, Proc. Nat. Acad. Sci. U.S.A., **72**, 3355 (1975).
78. A. D. Bender, C. E. Berkoff, W. G. Groves, L. M. Sofranko, G. R. Wellman, J.-H. Liu, P. P. Begosh, and J. W. Horodniak, J. Medicin. Pharmaceut. Chem., **18**, 1094 (1975).
79. D. K. Dikshit, R. C. Gupta, S. Kumar, C. M. Gupta, R. S. Kapil, K. Kar, V. P. Kamboj, and N. Anand, "IVth Indo-Soviet Symposium on the Chemistry of Natural Products, Lucknow, India, 1976", Abstracts, s. A, p. 22.
80. D. K. Dukshit, R. S. Kapil, and N. Anand, Indian J. Chem., **13**, 1353 (1975).
81. D. K. Dukshit, R. S. Kapil, and N. Anand, Indian J. Chem., **13**, 1359 (1975).
82. R. M. Scribner, Tetrahedron Letters, 3853 (1976).
83. N. A. Nelson and R. W. Jackson, Tetrahedron Letters, 3275 (1976).
84. R. C. Kelly, I. Schletter, and S. L. Stein, Tetrahedron Letters, 3279 (1976).
85. W. P. Schneider and R. A. Morge, Tetrahedron Letters, 3283 (1976).
86. K. Kühlein, A. Linkies, and D. Reuschling, Tetrahedron Letters, 4463 (1976).
87. D. Reuschling, M. Mitzlaff, and K. Kühlein, Tetrahedron Letters, 4467 (1976).
88. G. Ambrus and I. Barta, Prostaglandins, **10**, 661 (1975).
89. G. P. Rosing, T. J. H. Moinat, H. de Koning, and H. O. Huisman, Heterocycles, **4**(4), 719 (1976).
90. I. Vlattas, L. DellaVecchia, and A. Ong, J. Amer. Chem. Soc., 98, 2008 (1976).

91. E. I. Levkoeva, G. Ya. Shvarts, M. D. Mashkovskii, and L. N. Yakhontov, Khim. Farm. Zhur., (12), 64 (1976).
92. BRD. Appl. 2 452 536 (1976); Chem. Abs., 85, 46377 (1976).
93. BRD. Appl. 2 436 332 (1976); Chem. Abs., 84, 180023 (1976).
94. BRD. Appl. 2 460 977 (1976); Chem. Abs., 85, 177243 (1976).
95. BRD. Appl. 2 552 312 (1976); Chem. Abs., 85, 192576 (1976).
96. BRD. Appl. 253 682 (1976); Chem. Abs., 85, 5487 (1976).
97. US.P. 3 883 659 (1975); Chem. Abs., 84, 30855 (1976).
98. US.P. 3 975 399 (1976); Chem. Abs., 85, 192576 (1976).
99. Japanese P. 7 601 460 (1976); Chem. Abs., 85, 108516 (1976).
100. Japanese P. 7 604 166 (1976); Chem. Abs., 85, 94221 (1976).
101. Japanese P. 7 601 461 (1976); Chem. Abs., 85, 12375 (1976).

Ordzhonikdze All-Union Institute
of Chemistry and Pharmacology,
Moscow