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Heteroprostanoids: synthesis and biological activity

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ABSTRACT. Data on the synthesis and biological activity of the hetero analogues of prostaglandins are examined and systematised. The relationship between the structure and the activity of the heteroprostanoids is discussed.

The bibliography contains 170 references.

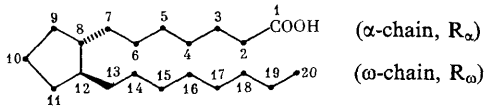
Contents

I. Introduction 243
II. Synthesis of heterocyclic prostanoids 244
III. Heteroanalogues of the α- and ω-chains 249
IV. Heteroanalogues of secoprostanoids 253
V. Heteroanalogues of cyclic endoperoxides 255
VI. Heteroanalogues of prostacyclin 256
VII. Biological activity of the heteroprostanoids 259

I. Introduction

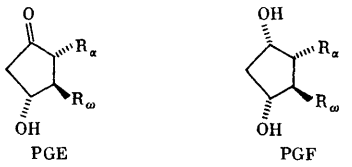
The prostaglandins (PG) are a unique class of natural low molecular bioregulators which are synthesised in practically all tissues and organs of animals and man and play an extremely important role in normal functioning and pathology.

In chemical structure they are unsaturated polyhydroxy acids, derivatives of the hypothetical twenty-atom prostanoic acid.

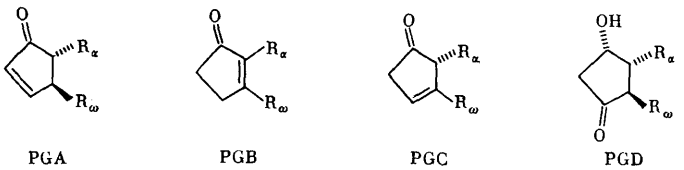


prostanoic acid

The C_7-carboxyalkyl chain of prostaglandins is known as the α-chain and the C_8 alkyl the ω-chain. The character of the functionality of the five-membered ring determines the type of prostaglandins. Prostaglandins of the E and F type are referred to as primary PG and prostaglandins of types A, B, C and D form the group of secondary PG.



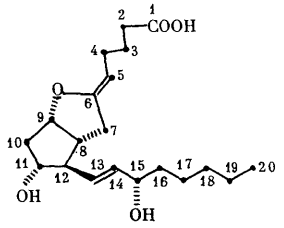
primary PG



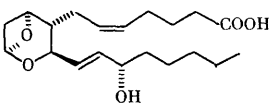
secondary PG

Three series of natural PG can be distinguished. The first is characterised by the presence of one Δ^{13}-*trans*-double bond, the second contains an additional Δ^5-*cis*-double bond. The PG of the third series contain a further Δ^{17}-*cis*-double bond in addition to those mentioned. The number of multiple bonds in the side chains corresponds to the subscript number (PGE_1, PGE_2 etc.).

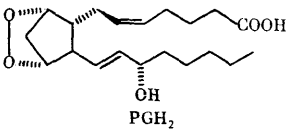
Prostacyclin (PGI_2), 6,9α-epoxy-11α,15α-dihydroprosta-5(*Z*),13(*E*)-dienoic acid, prostaglandin endoperoxides (PGG_2, PGH_2) and thromboxane (TxA_2), like the primary PG, are biosynthetic products of the arachidonic acid cascade and the most important biomolecules of its metabolism.



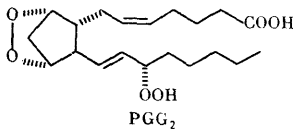
prostacyclin (PGI_2)



thromboxane A_2 (TxA_2)



PGH_2



PGG_2

prostaglandin endoperoxides

The extremely low content of PG, cyclic endoperoxides and prostacyclin in nature, the exceedingly wide spectrum of biological action and the chemical and metabolic instability of preparations based on them, are factors stimulating the development of synthetic

methods for obtaining these and modified compounds (analogues of the natural prototypes) with more specific and prolonged action for the needs of medicine and agriculture.

The heteroprostaglandins occupy an important place among the multitude of analogues synthesised. These are compounds in which one or several carbon atoms of the prostanoid skeleton are replaced by heteroatoms (nitrogen, oxygen, sulphur). The synthesis and biological activity of such compounds form the subject of the present review. Also considered are the heteroanalogues of the cyclic endoperoxides (PGH) and prostacyclin (PGI) in which the oxygen atoms of the endoperoxide and the *cis*-enol ether fragments are replaced in addition to replacing carbon atoms of the skeleton by nitrogen and sulphur.

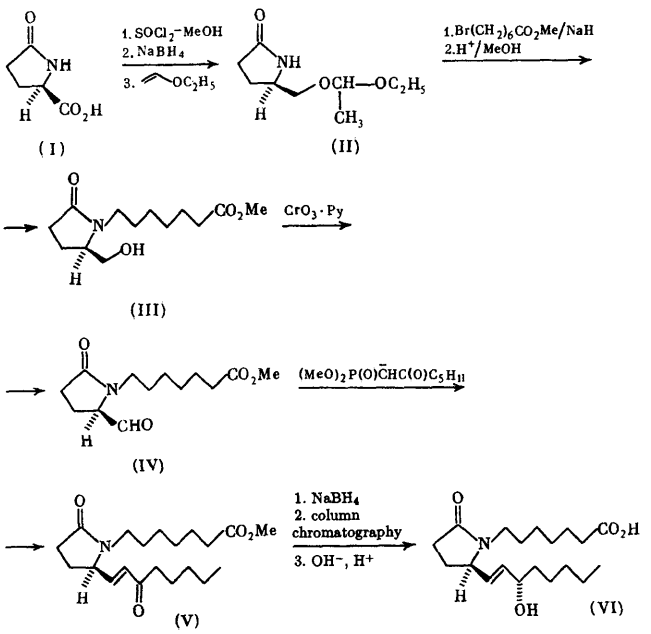
In contrast to the reviews published previously,[1-3] which are devoted mainly to detailed analysis of actual synthetic schemes for PG heteroanalogues, cyclic endoperoxides and prostacyclin, attention is paid in the present review chiefly to an analysis of the methodology of forming the heteroprostanoid skeleton and also to the dependence of biological properties on structure.

II. Synthesis of heterocyclic prostanoids

Construction of the heteroprostanoid skeleton is based on the following main approaches: 1) the regio- and stereoselective introduction of the side chains (R_α and R_ω) or fragments of them into the appropriate heterocyclic compounds, 2) synthesis based on acyclic long chain precursors bearing the side chains or intermediates when the heterocyclic system is formed in one of the intermediate or at the very last stage of the synthesis, 3) regioselective introduction of the heteroatom into the cyclic portion of the prostanoid skeleton of 11-norprostanoids.

1. Heteroprostanoids based on heterocyclic precursors

This approach is widely used in the synthesis of heterocyclic prostanoids. It may be illustrated by the preparation of optically active (12*R*,15*S*)-(–)-11-deoxy-8-aza-PGE$_1$ (VI) from (*R*)-(+)-pyroglutamic acid (I).[4]



(I) (II) (III) (IV) (V) (VI)

After conversion into the (*R*)-ethoxyethyl ether (II) the latter is alkylated with methyl 7-bromoheptanoate. The alcohol (III) formed by removing protection was oxidised (Collins) to the (*R*)-aldehyde (IV). A Wittig reaction of the synthon (IV) with dimethyl-2-keto-heptylphosphonate gives the (*R*)-enone (V) which on reduction with sodium borohydride leads to a mixture of the 15-epimers of the desired 8-azaprostanoid. Chromatographic resolution of the latter and mild hydrolysis of the ester group in the 15*S*-isomer completes the synthesis of (12*R*,15*S*)-11-deoxy-8-aza-PGE$_1$ (VI).

Other examples are given in Table 1 of heteroprostanoids obtained using analogous schemes published in the last 10–12 years. In the majority of cases the α-chain in the heterocyclic precursor is introduced using classical methods of *N*- and *C*-alkylation (or acylation). The ω-chains in the alkylation products are formed using the Wittig–Horner–Emmons phosphonate condensation after transformation of the functional groups in position 12 (PG nomenclature) into an aldehyde.

Table 1. Heteroprostanoids from heterocyclic precursors.

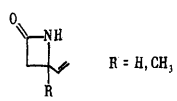
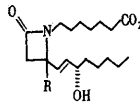
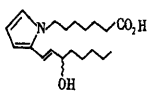
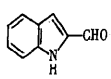
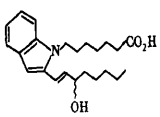
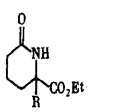
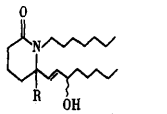
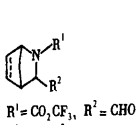
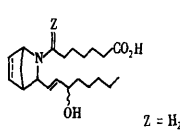
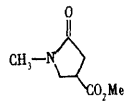
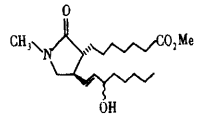
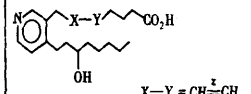
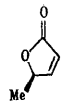
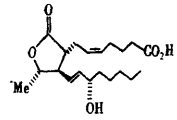
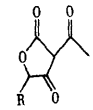
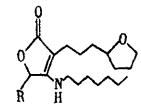
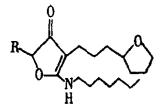
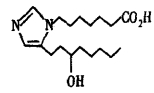
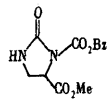
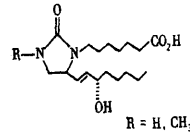
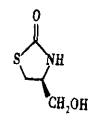
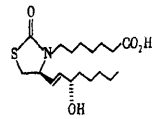
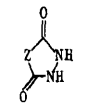
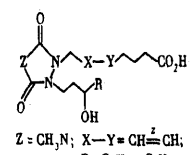
Type of heteroprostanoid	Initial heterocyclic precursor	Structural formula	Reference
8-Aza-	 R = H, CH$_3$	 R = H, CH$_3$	[5]
			[6]
			[6]
	 R = H, CH$_3$	 R = H, CH$_3$	[7]
	 R^1 = CO$_2$CF$_3$, R^2 = CHO R^1 = Ts, R^2 = CO$_2$Bu	 Z = H$_2$ Z = O	[8, 9]

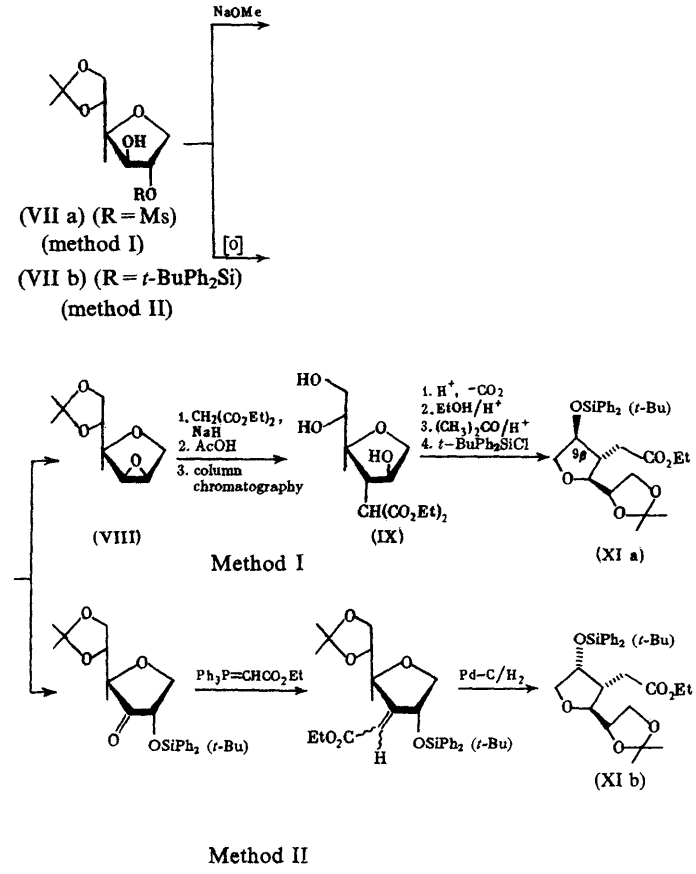
Table 1 (continued).

Type of heteroprostanoid	Initial heterocyclic precursor	Structural formula	Reference
10-Aza-			[10]
		 X—Y = CH=CH, CH_2—CH_2	[11]
10-Oxa-			[12]
10-Oxa-13-aza-			[13]
11-Oxa-13-aza-	R = H, CH_3		
8,10-Diaza-			[14]
		 R = H, CH_3	[15]
8-Aza-10-thia-			[16]
8,10,12-Triaza-		 Z = CH_3N; X—Y = CH=CH; R = C_5H_{11}, C_6H_{13}. Z = S; X—Y = CH_2—CH_2; R = *cyclo*-C_6H_{11}	[17 18]
10-Thia-8,12-diaza-	Z = CH_3N		

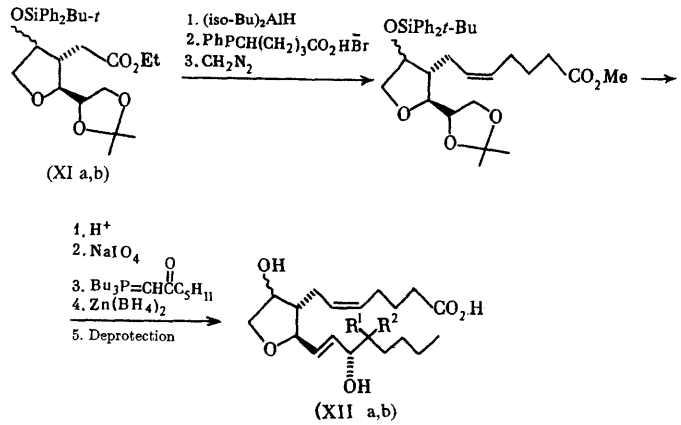
This approach also includes a set of schemes for the synthesis of 11-oxaprostanoids of the $F_{2\alpha(\beta)}$ series from natural heterocyclic compounds, viz. sugars and dihydrosugars.[19–21] The furan ring of the latter is a convenient intermediate for the heterocyclic system for PG 11-oxa analogues. The side chain *cis*-diol, or another analogous group, in the vicinity of the heteroatom of the ring serves as a precursor of the aldehyde function necessary for forming the ω-chain.

The key stage of forming the 11-oxaprostanoid structure from sugars (dihydrosugars) is the replacement of their C(3) hydroxy group by an ethoxycarbonylmethylene group which is an α-chain intermediate. This replacement may be effected by two methods.

In the synthesis of 11-oxa-$PGF_{2\alpha(\beta)}$ prostanoids (XIIa, b) from derivatives of 1,4-anhydro-D-glucitol (VIIa, b) [19] method I includes the addition of malonic ester to the epoxide (VIII) with isolation of the desired regioisomer (IX) and its subsequent hydrolysis and decarboxylation. Method II comprises the selective oxidation of the C(3) hydroxyl group with subsequent treatment of the resulting 3-keto derivative with the appropriate phosphorane and stereoselective reduction of the exocyclic multiple bond in compound (X). It must be noted that the method of introducing the ethoxycarbonylmethyl group determines the stereochemistry of the chiral centre at position 9 (PG nomenclature).

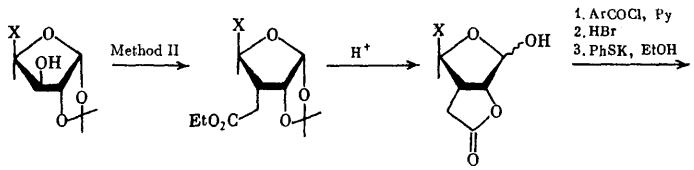


The diastereomeric synthons (XIa, b) were used for obtaining the desired heteroprostanoids by a sequence of classical conversions.

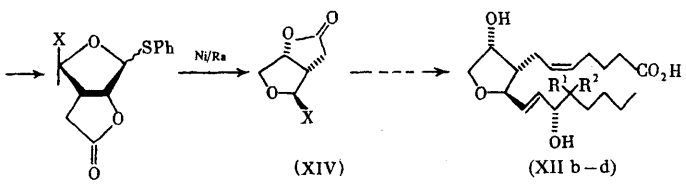


a) 9β–OH, b) 9α–OH ($R^1=R^2=H$)

In the synthesis of 11-oxaprostanoids (XIIb–d) from derivatives of D-xylose (XIIIa) and D-glucose (XIIIb),[20] after introducing the ethoxycarbonylmethyl group by method II and acid hydrolysis, the C(1)-glycosidic hydroxyl group was eliminated via the phenylthio derivative by hydrogenolysis over Raney nickel with the formation of oxa analogues of the Corey lactone (XIV).

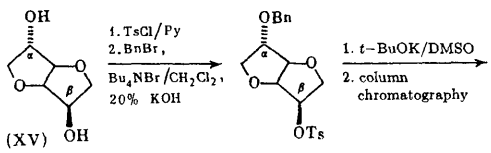


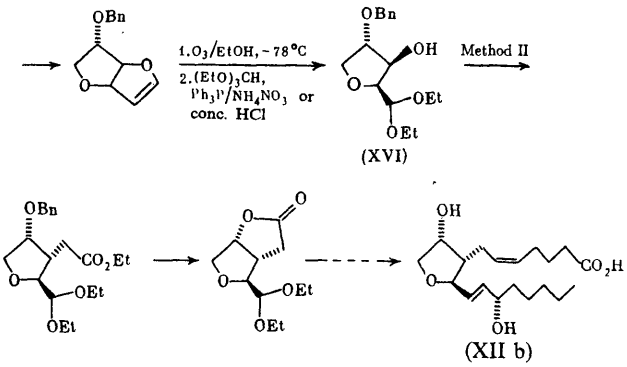
(XIII a,b): a) $X=CH_2OCH_2Ph$, b) X=



b) $R^1=R^2=H$, c) $R^1=H$, $R^2=CH_3$, d) $R^1=R^2=CH_3$

An analogous approach was used in the synthesis of 11-oxa-$PGF_{2\alpha}$ (XIIb) starting from 1,4:3,6-dianhydro-D-sorbitol (XV),[21] which was transformed into furanol (XVI) by a known series of conversions.



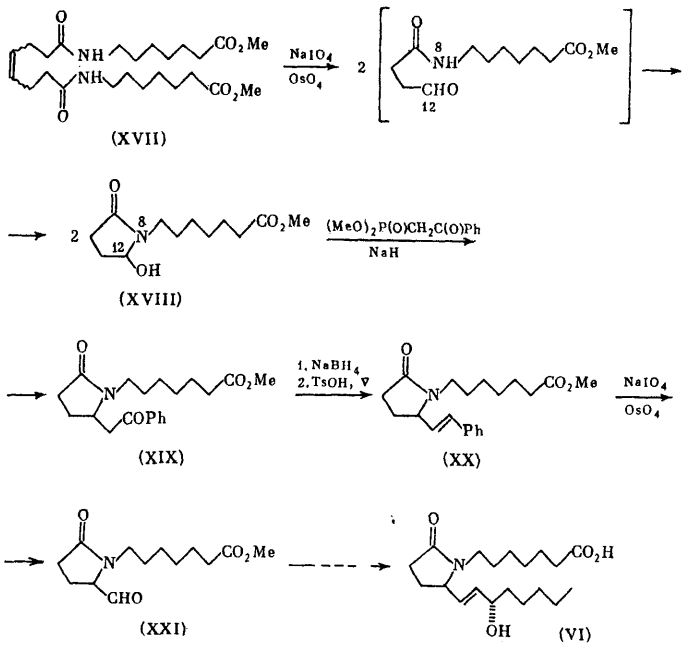


2. Heterocyclic prostanoids from acyclic precursors

Depending on the molecular fragments used to form the heterocyclic systems, the schemes of synthesis of the heterocyclic prostanoids from acyclic precursors may be subdivided into five main groups, i. e. schemes including 8,12, 8,9, 9,10, 10,11 and 11,12 closure of the heterocycle.

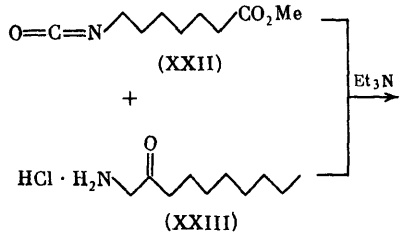
a) Schemes utilising 8,12 closure of the heterocycle

When obtaining the key synthon 11-deoxy-8-azaprostanoids (XXI) from the diamide (XVII), the cyclisation of the long chain precursor occurs after oxidative fission of the (*E,Z*)-multiple bond in the latter. Condensation of the resulting cyclic lactam (XVIII) with the sodium salt of dimethyl phenacylphosphonate gives the ketolactam (XIX). The sequence of conversions (XIX)–(XX)–(XXI) leads to the synthon (XXI).[22]



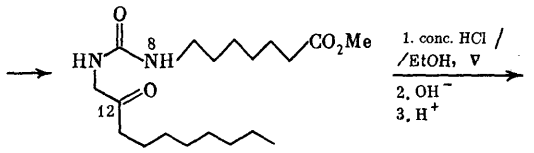
The initial components in the synthetic scheme for the 11,12-dehydro-8,10-diazaprostanoid (XXV) from the isocyanate (XXII) and the β-aminoketone (XXIII) carry the side chains in an already finished form. The formation of the heterocyclic system

occurs in two stages in this case, through the initial formation of the adduct (XXIV) and its subsequent cyclisation.[23]

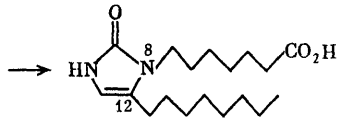


(XXII)

(XXIII)



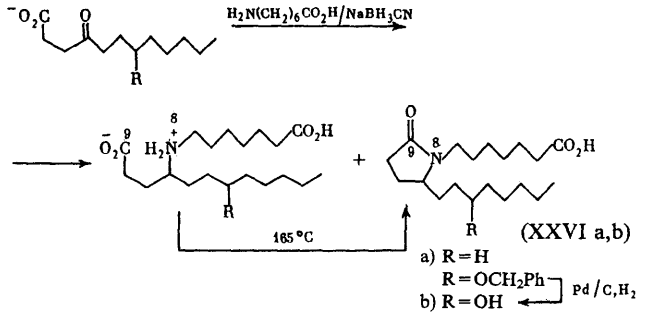
(XXIV)



(XXV)

b) Schemes utilising 8,9 and 11,12 closure of the heterocycle

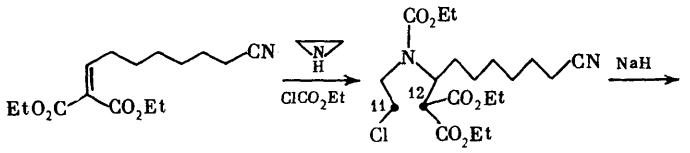
The formation of the heterocycle in the synthesis of 8-aza-9-keto-prostanoic acid (XXVIa) and its 15-hydroxy derivative occurs after the formation (and in part simultaneously with the formation) of the α-prostanoid chain (8,9 closure of the heterocycle).[23]

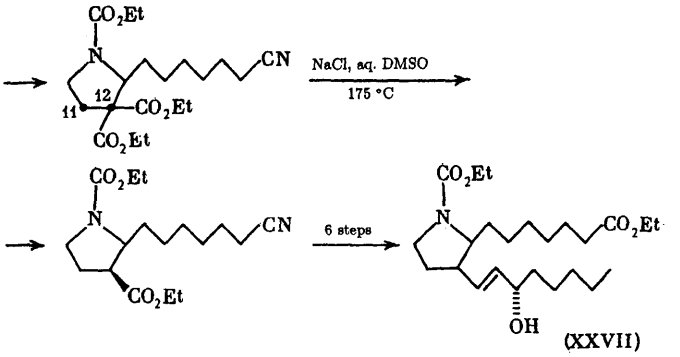


(XXVI a,b)

The 11,12 closure of the heterocycle utilises the previously known schemes of synthesis of the 9-aza- (XXVII) and 9-thia- (XXVIII) prostanoids. The key stages are the following:

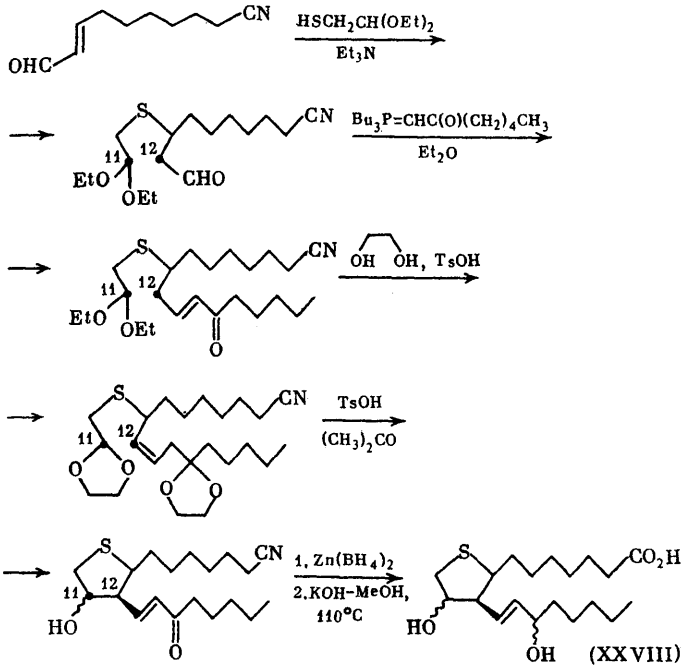
9-*N*-carbethoxy-11-deoxy-PGE$_1$ (XXVII) [24]





(XXVII)

9-deoxy-9-thia-PGE$_1$ (XXVIII) [25]

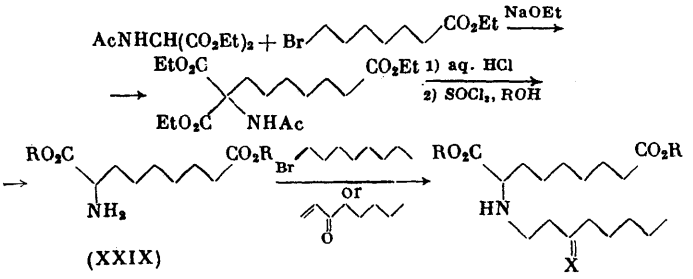


(XXVIII)

As is evident from the schemes the heterocyclic fragment may be formed at various stages of building the prostanoid skeleton.

c) Schemes utilising 9,10 and 10,11 closure of the heterocycle

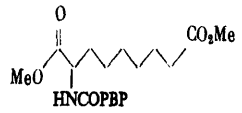
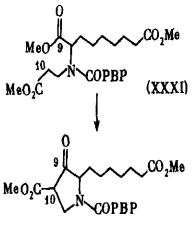
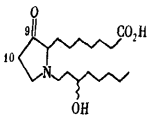
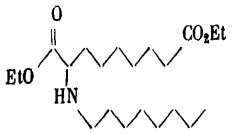
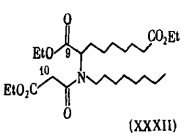
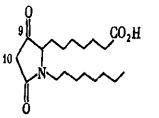
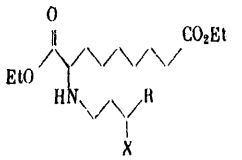
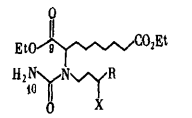
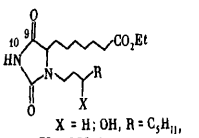
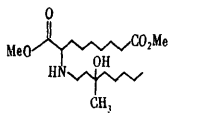
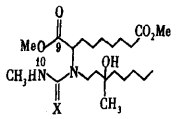
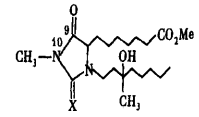
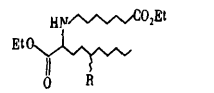
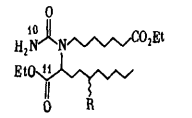
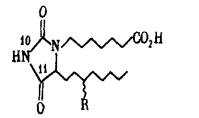
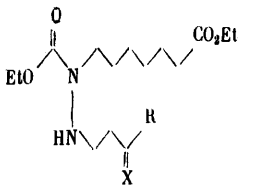
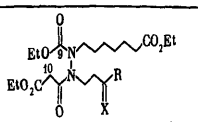
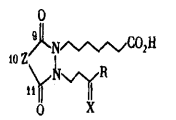
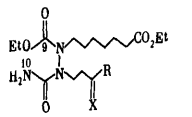
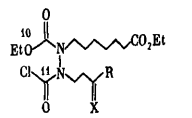
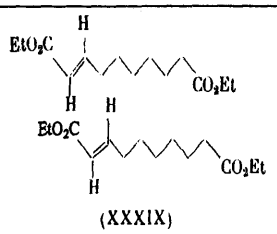
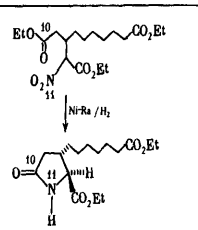
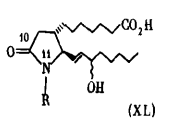
Schemes for obtaining prostanoids with nitrogen atoms at the junction positions of the ring and the side chains mainly belong to this group. The key synthons for these heteroanalogues are long chain α-amino esters and amino diesters, the standard synthetic scheme for which is shown using the examples of amino diesters of azelaic acid (XXIX) and their *N*-alkyl derivatives (XXX).[26]



(XXIX)

(XXX) (X = H_2, O)

Table 2. Synthesis of heteroprostanoids, including 9,10 and 10,11 closure of the heterocycle.

Type of heteroprostanoid	Precursor	Reagent	Condensation product	Structural formula	Reference
12-Aza-			 (XXXI)		[27]
		$HO_2CCH_2CO_2Et$, DCCI	 (XXXII)		[26]
10,12-Diaza-		HCNO	 (XXXIII)	 X = H; OH, R = C_5H_{11}, X = OH, R = *cyclo*-C_6H_{11}	[28–30]
		MeNCO or MeNCS	 X = O, S (XXXIV)	 X = O, S	[31]
8,10-Diaza-		HCNO	 (XXXV)	 R = H; OH	[29]
8,12-Diaza-, 8,10,12-diaza-, 10-oxo-8, 12-diaza-		$EtO_2CH_2CO_2H$, DCCI	 (XXXVI)	 Z = CH_2, NH, O; X = H; H, OH; R = C_5H_{11}, *cyclo*-C_6H_{11}	[18]
		HCNO	 (XXXVII)		
		$COCl_2$	 (XXXVIII)		
11-Aza-	 (XXXIX)	$O_2NCH_2CO_2Me$, Triton B		 (XL) R = H, Me	[32]

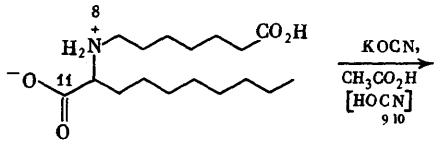
Examples are given in Table 2 of the preparation of heteroprostanoids using these and related synthons.

A characteristic of this group of schemes is the formation of the products (XXXI)–(XXXVIII) by the condensation of a series of reactants at the nitrogen atom of the amino diesters and a cyclisation stage. It must be indicated that for certain schemes, including thermal cyclisation, assignment to this group is arbitrary since the preparation of condensation products and closure of the heterocycle is usually carried out in one step.

The scheme for obtaining 11-azaprostanoids (XL) from the precursor (XXXIX) is also assigned to this type.

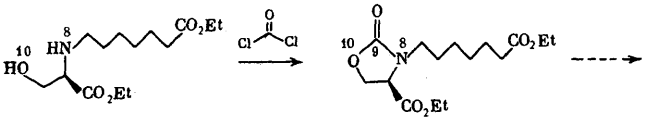
d) Schemes utilising mixed closure of the heterocycle

The synthesis of the 8,10-diaza (XLI), 10-oxa-8-aza (XLII) and 10-oxa (XLIII) analogues does not include the formation of condensation products of type (XXXI)–(XXXVIII). The overall reaction is as though the reagent was inserted between positions 8,11, 8,10 and 10,12 of the long chain prostanoid precursors [(8,9 + 10,11), (8,9 + 9,10) and (10,11 + 11,12) closure of the heterocycle respectively].



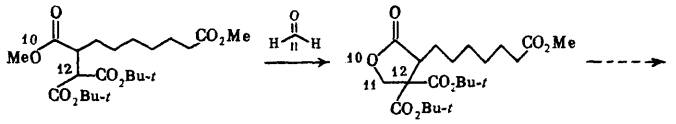
[Ref. 23]

(XLI)



[Ref. 33]

(XLII)



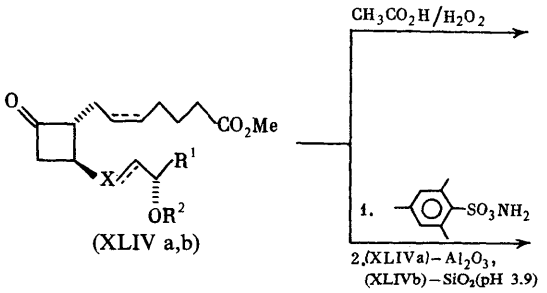
[Ref. 34]

(XLIII)

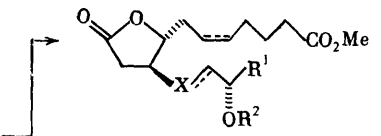
Examples are given in Table 3 of the formation of heterocyclic prostanoid fragments from long chain synthons containing vicinally located functional groups or a double bond in positions 8 and 12 of the future prostanoid structure. Closure of the heterocycles in the analogues being considered are (9,10 + 10,11) and (8,9 + 11,12).

3. Heterocyclic prostanoids from PG 11-nor analogues

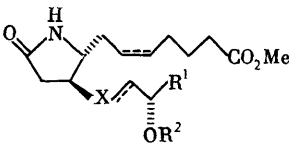
The ring expansion reaction of 11-norprostanoids (XLIVa, b) was used in the synthesis of 9-oxa (XLVa) and 9-aza (XLVIa) analogues of PGE_2 and also 9,13-dioxa- (XLVb) and 13-oxa-9-aza- (XLVIb) prostanoids. In all cases the introduction of the heteroatom into the prostanoid skeleton occurred with complete regioselectivity.[5,41]



(XLIV a,b)



(XLV a,b)



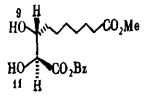
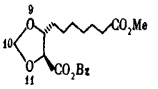
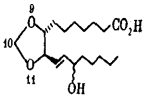
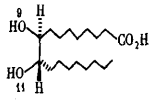
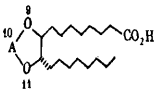
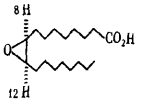
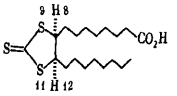
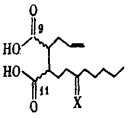
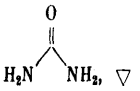
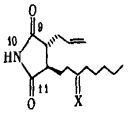
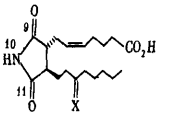
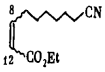
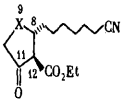
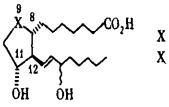
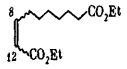
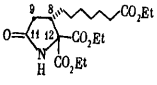
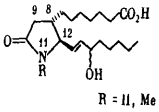
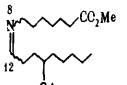
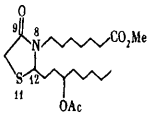
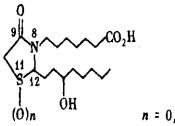
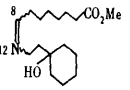
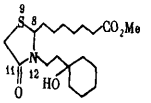
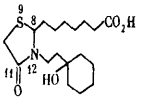
(XLVI a,b)

a) X = CH=, $R^1 = -C_5H_{11}$, $R^2 = -H$;
b) X = O–, $R^1 = -CH_2OPh$, $R^2 = -H$, $-SiMe_2(t\text{-Bu})$

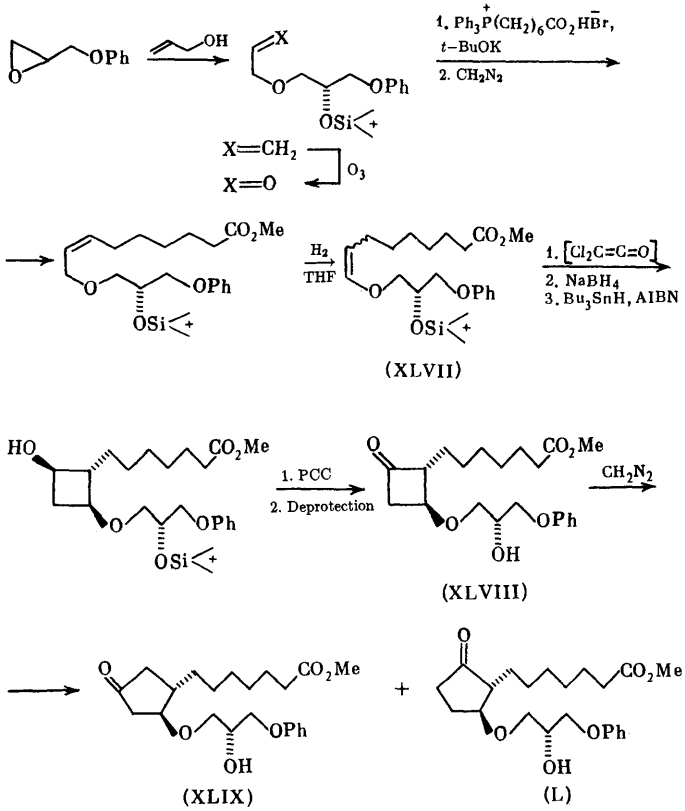
III. Heteroanalogues of the α- and ω-chains

The synthesis of the 13-oxaprostanoids (XLVIII)–(L) is based on the initial formation of the vinyl ether (XLVII) carrying both prostanoid chains with the heteroatom in the appropriate position. Construction of the cyclic portion of prostanoid (XLVIII) occurs as

Table 3. Synthesis of heteroprostanoids by a mixed closing of the heterocycle.

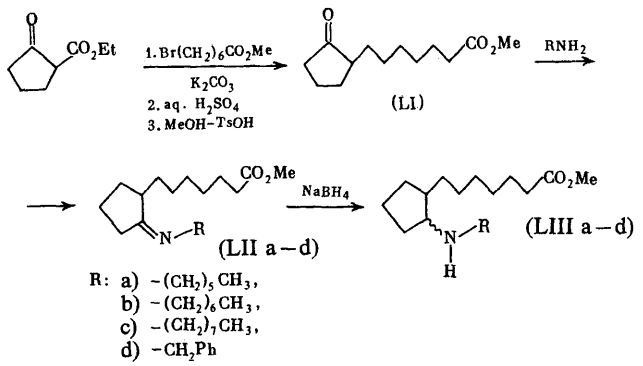
Type of heteroprostanoid	Long-chain bifunctional precursors	Reagents	Cyclisation products	Structural formula	Reference
9,11-Dioxa-		$(CH_2O)_n$			[35]
		$(CH_2O)_n$, $COCl_2$, $CSCl_2$, $POCl_3$/MeOH, $SOCl_2$		 A: CH_2, C(O), C(S), P(O)OCH_3, S(O)	[36]
9,11-Dithia-					[36]
10-Aza-	 X = H_2, O		 X = H_2, O	 X = H_2, O	[37]
9-Oxa-(thia)-		$NaXCH_2CO_2Et$, X=O, S		 X = O, X = S	[38, 39]
11-Aza-		$AcNHCH(CO_2Et)_2$, EtONa		 R = H, Me	[32]
8-Aza-11-thia-		$HSCH_2CO_2Me$		 n = 0, 2	[23]
9-Thia-12-aza-					[40]

a result of a [2 + 2] cycloaddition reaction of dichloroketene to the ether obtained.[41]

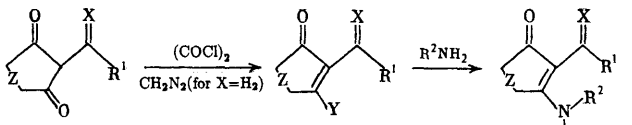


However functionalised five-membered precursors are used in the majority of schemes for the synthesis of 7- and 13-heteroprostanoids. The heteroatom may be introduced into the composition of the former or into a functional group of a fragment of the prostanoid chains.

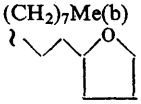
The key stage in the formation of the heteroprostanoid fragment of the 13-azaprostanoids (LIIIa–d) is the addition of aliphatic amines at the carbonyl group of the keto ester (LI) with subsequent reduction of the resulting azomethines (LIIa–d).[42]



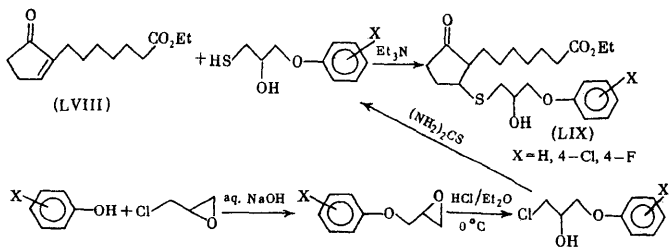
The overall key stage in the synthesis of the 13-aza-, 7-keto-13-aza- and 13-keto-7-azaprostanoids (LVIIa–g) from the cyclic β-di- and β-triketones (LIVa–g) is the addition of an amine to the enol ether (LV) or to the ketovinyl chloride (LVIa–g).[13,43]



(LIV a–g) (LV)(Y = OMe, X = H_2, R^1(c))
(R^1 = a–c) (LVI a–g)(Y = Cl, R^1 = a–c) (LVII a–g)

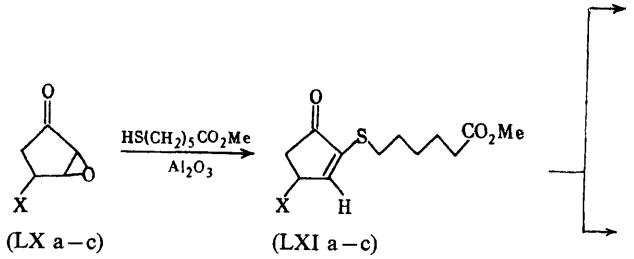
(LVII)	Z	X	R^1	R^2
a	–	O	$(CH_2)_4CO_2Et$(a)	$(CH_2)_7Me$
b	–	O	$(CH_2)_4CO_2Et$	CH_2Ph
c	–	O	$(CH_2)_7Me$(b)	$(CH_2)_5CO_2Me$
d	–	H_2	 (c)	$(CH_2)_6Me$
e	CH_2	O	$(CH_2)_4CO_2Et$	$(CH_2)_7Me$
f	CH_2	O	$(CH_2)_4CO_2Et$	CH_2Ph
g	CH_2	O	$(CH_2)_7Me$	$(CH_2)_5CO_2Me$

The most widespread method of forming 13-thiaprostanoids includes the addition of mercaptans, corresponding to the ω-chain, to the multiple bond of 2-alkyl substituted cyclopentenones. For example 13-thia-16-aryloxy-17,18,19,20-tetranor-PGE_1 (LIX) was synthesised from the classical synthon (LVIII).[44]

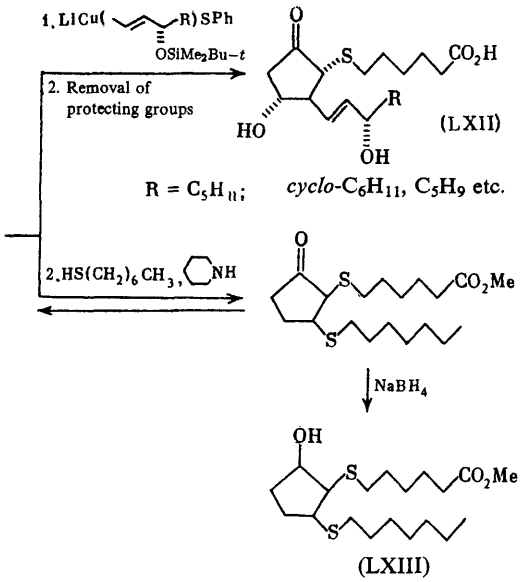


An analogous scheme was used in the synthesis of the bicyclic 13-thiaprostanoids,[45] and also 11-hydroxy-13-thia analogues.[46]

The 7-thiaprostanoids (LXII) were obtained from the cyclic epoxyketones (LXb, c).[47,48] The addition of a mercaptan corresponding to the structure of the ω-prostanoid chain to the enone (LXIa) leads to a 7,13-dithiaprostanoid of low stability due to a retro-Michael reaction. Reduction of the 9-keto group gives the stable analogue (LXIII).[49]

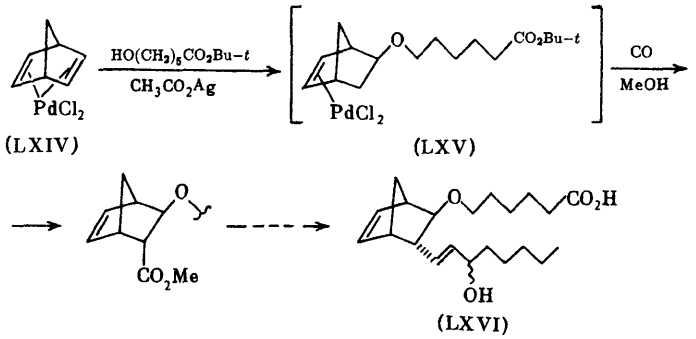


a) X = H,
b) X = OTHP,
c) X = OSiMe$_2$(*t*-Bu)

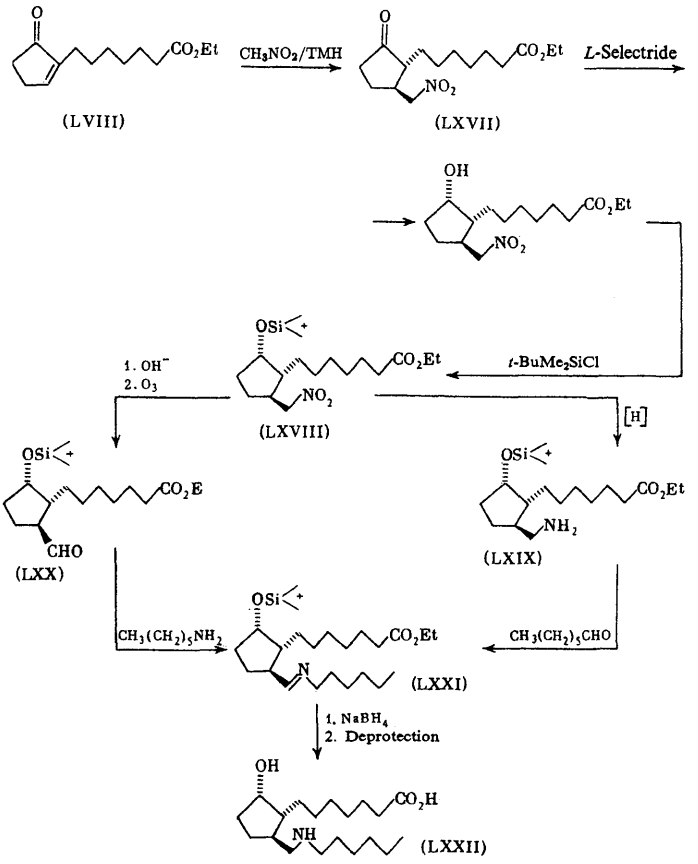


The most widely used approach to obtaining 7-oxa-PG analogues is the alkylation of cyclopentanoid synthons at the 8-hydroxyl function with alkyl halides corresponding to the α-chain structure.[50]

The bicyclic 7-oxaprostanoid (LXVI) was obtained by oxypalladation of the norbornadiene complex (LXIV) with ε-hydroxycaproic ester and subsequent direct carbonylation of the intermediate (LXV).[51]



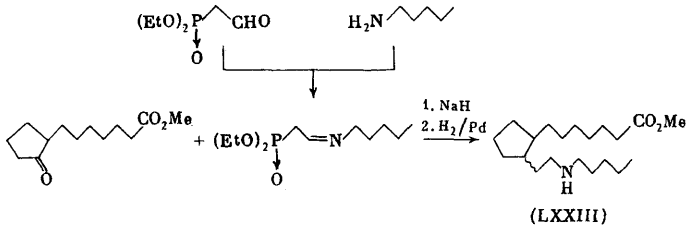
The principle of constructing sidechains analogous to that considered for 7- and 13-heteroprostanoids with other positions of the heteroatom may be illustrated by the example of the synthesis of the 14-azaprostanoid (LXXII).[52] The Michael addition of nitromethane to the cyclopentenone (LVIII) leads to the nitromethyl derivative (LXVII). After the selective reduction of the 9-keto group with L-Selectride and protection of the resulting alcohol, the formation of the ω-chain is effected by two methods. One is by reduction of the nitro group in compound (LXVIII) and subsequent condensation of the amino derivative (LXIX) with hexanal. The other is by the ozonolysis of the nitronate of the ester (LXVIII) with the formation of the aldehyde (LXX) and its further reaction with hexylamine. The final stage of the synthesis is the borohydride reduction of the azomethine (LXXI) formed in both cases.



Methods which have been used to join fragments of the heteroprostanoid chains include nucleophilic substitution of tosylates (mesylates) with the appropriate alkyl sulphides (13, 14 and 15-thiaprostanoids[53]), radical and Michael addition of alkyl mercaptans at a terminal multiple bond (4-thia, 5-thia and 6-thia analogues[48]), alkylation of phenoxides or alkoxides with various alkyl halides (3-oxaprostanoids[54]), alkoxyenamination with a hemiacetal (4-oxa-5-azaprostanoids[55]) and the formation of amide (13- and 14-aza- [56,57]) and sulphonamide bonds (benzenesulphonamidoprostanoids[57–62]).

An alternative approach to prostanoids of this type is the addition of an independently formed heteroprostanoid chain to a

cyclopentanoid synthon as in the synthesis of the 15-azaprostanoid methyl ester (LXXIII).[42]



(LXXIII)

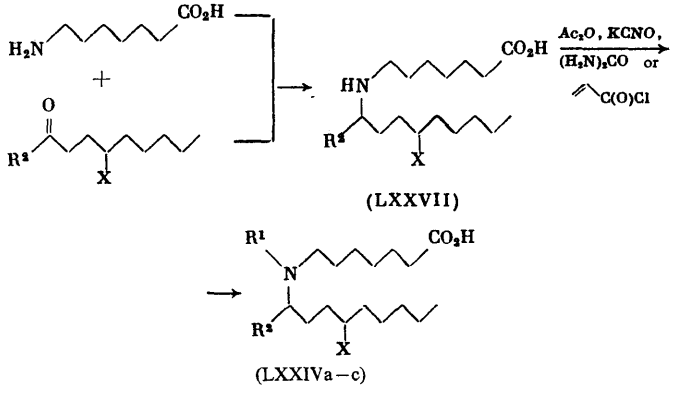
IV. Heteroanalogues of secoprostanoids

From the point of view of structural features the secoprostanoids are as though the acyclic precursors of prostanoids. Nevertheless such 'unfinished prostanoids' display marked prostaglandin-like activity. This group of biologically active compounds did not receive attention in the previous reviews so we saw the need to deal with this problem.

The synthesised heteroanalogues are referred to as 11,12-,[63–67] 8,12-[68,69] and also furan-containing secoprostanoids.[70]

The 11,12-secoprostanoids are mainly *N*-acyl-*N*-alkyl-7-aminoheptanoic acids of the type of (LXXIVa–c), 7-(*N*-alkylmethanesulphonamido)heptanoic acids (LXXIVd), 8-alkylthio(sulphinyl, sulphonyl)-12-hydroxyacids (LXXVa–c), and also 8-acetyl-12-hydroxy-13-aryloxy(thioaryl, alkoxy)tridecanoic acids (LXXVIa, b).

The heteroanalogues (LXXIVa–c) were obtained through the reductive alkylation of 7-aminoheptanoic acid with aldehydes and ketones corresponding to the ω-prostanoid chain and subsequent reaction of the resulting substituted aminoheptanoic acids (LXXVII) with acetic anhydride, potassium cyanide, urea or acryloyl chloride.[63]



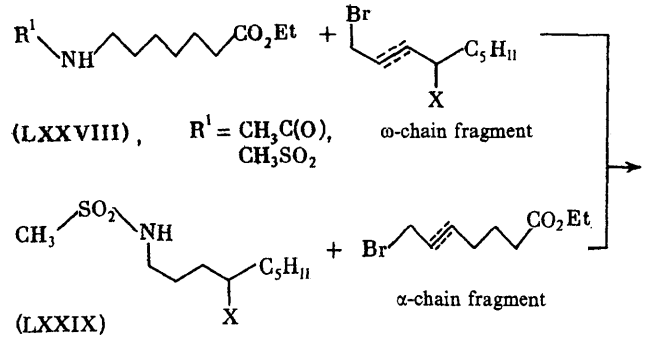
(LXXVII)

(LXXIVa–c)

a) $R^1 = CH_3C(O)$, b) $R^1 = H_2NC(O)$,

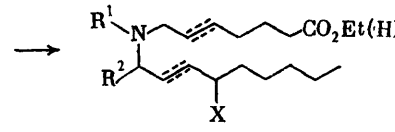
c) $R^1 = \text{cyclopropyl-C(O)}$; $R^2 = H, Ph, CH_3$; $X = H$

An alternative variant is the alkylation of the acetyl- and methanesulphonylamides (LXXVIII) and (LXXIX) with halogen derivatives corresponding to the structure of the α- or ω-prostanoid chain.[63,64]



(LXXVIII), $R^1 = CH_3C(O), CH_3SO_2$; ω-chain fragment

(LXXIX); α-chain fragment

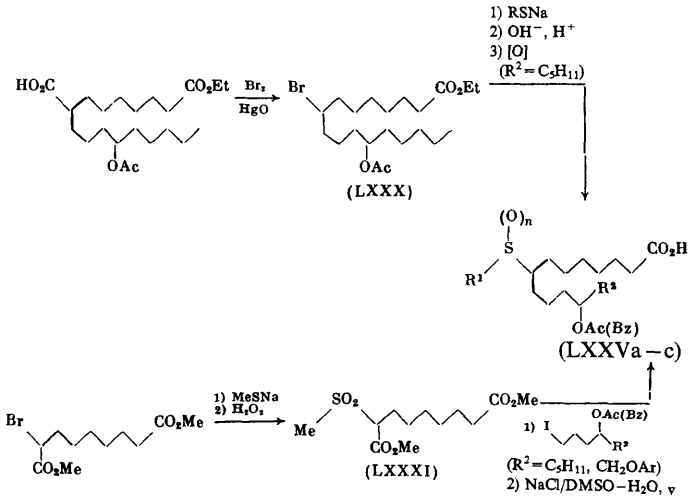


(LXXIV a,d)

a) $R^1 = CH_3C(O)$, $R^2 = H$;

X = H, OAc(OH) d) $R^1 = CH_3SO_2$, $R^2 = H$

The secoprostanoids (LXXVa–c) are formed by the reaction of haloester (LXXX) with various thiolates and also by alkylation of the sulphone (LXXXI).[65]



(LXXX)

(LXXXI)

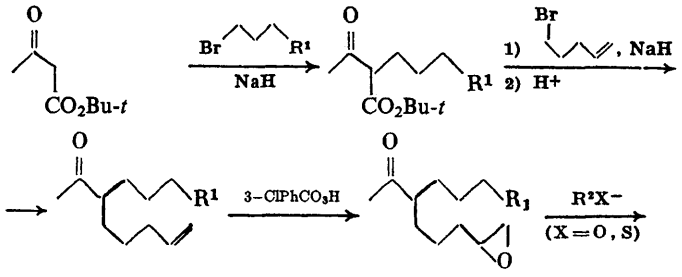
(LXXVa–c)

a) $n = 0$ to 2, $R^1 = Me$, $R^2 = C_5H_{11}$;

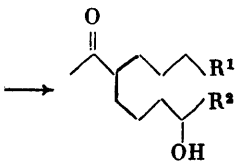
b) $n = 0.2$, $R^1 = HO(CH_2)_2$, $R^2 = C_5H_{11}$;

c) $n = 2$, $R^1 = Me$, $R^2 = CH_2OAr$.

The 8-acetyl-12-hydroxy-13-aryloxy(thioaryl, alkoxy)tridecanoic acids (LXXVIa, b) were obtained from the key synthons (LXXXII) through epoxidation of the latter and fission of the epoxide ring with phenoxides, phenylthiolates and alkoxides.[66,67]

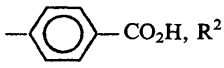


(LXXXII)



(LXXVIa, b)

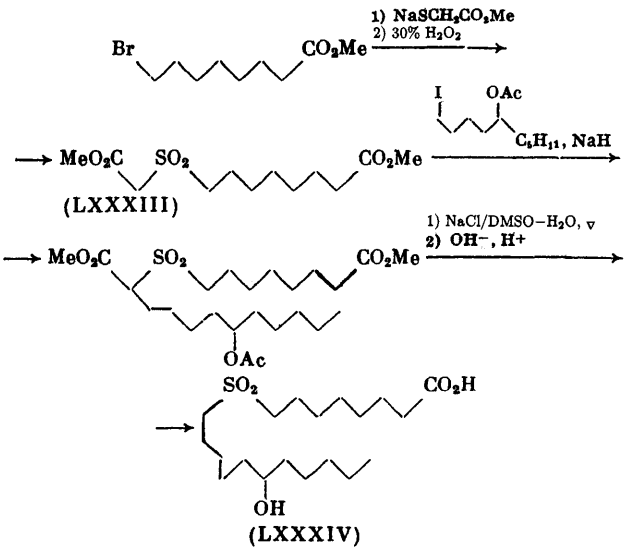
a) $R^1=(CH_2)_3CO_2H$, $R^2=CH_2OAr(CH_2SAr)$;

b) $R^1=$  CO_2H, $R^2=CH_2O(CH_2)_2Me$.

A series of 7-*N*-alkylmethanesulphonamide secoprostanoids, containing *O*- and *S*-phenylene fragments in the ω-chain, was obtained from the methanesulphonamide (LXXVIII), $R^1 = MeSO_2$ using an analogous approach.[66]

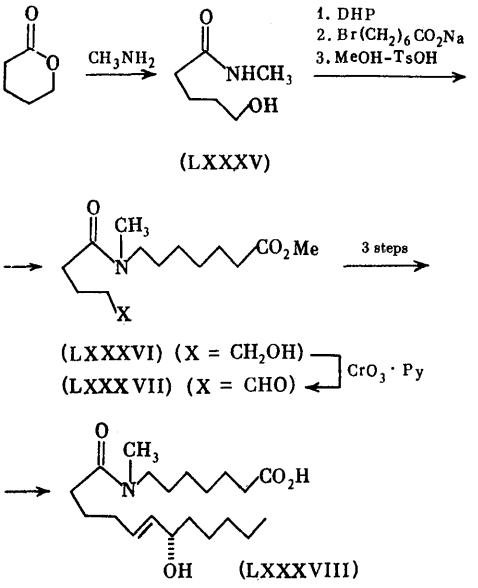
Analogues of 8,12-secoprostanoids synthesised include the 9-sulphonyl (LXXXIV),[65] 8-aza (LXXXVIII), 10-oxa (XC) [68] and the 10-aza and 8-oxa analogues.[69]

The key stage in the formation of the sulphonyl analogue (LXXXIV) is the alkylation of the diester (LXXXIII) in the α-position with an ω-prostanoid chain fragment.[65]



(LXXXIV)

The 8-azasecoprostanoid (LXXXVIII) was obtained through fission of δ-valerolactone with methylamine to form (LXXXV), alkylation of the latter with 7-bromoheptanoic acid, oxidation of the hydroxyl function in the derivative (LXXXVI) and formation of the ω-chain from the aldehyde (LXXXVII) by classical methods.[68]



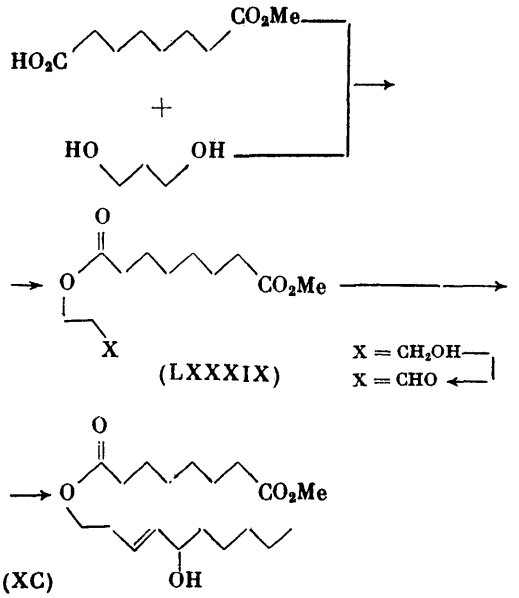
(LXXXV)

(LXXXVI) (X = CH_2OH)

(LXXXVII) (X = CHO)

(LXXXVIII)

The 10-oxa analogue (XC) was synthesised from the hydroxy ester (LXXXIX) to which the ω-chain was attached in an analogous manner.[68]



(LXXXIX)

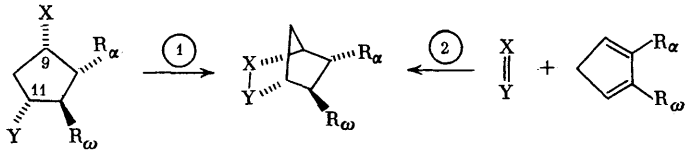
(XC)

The principle of forming the 10-aza- and 8-oxasecoprostanoids was analogous to that considered for the 8-aza and 10-oxa analogues.[69]

V. Heteroanalogues of cyclic endoperoxides

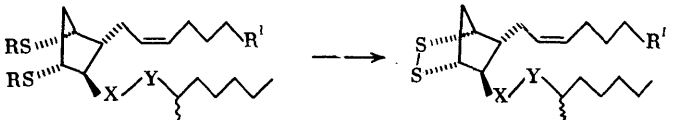
The main problem in the synthesis of heteroanalogues of the cyclic endoperoxides (PGH, PGG) is the replacement of the chemically unstable cyclic endoperoxide group by a more stable one. Of the large number of PGH and PGG analogues obtained up to the present time only those in which one or both oxygen atoms of the endoperoxide grouping are replaced by other heteroatoms (nitrogen, sulphur) are considered in the review.

The formation of the appropriate endocyclic bridging groups of such analogues is effected by two main approaches. The first is through the chemical bond of the functional groups at positions 9,11 of the prostanoid molecule and the second is through a 1,4-cycloaddition of dienophiles, carrying a bridging group in some form or other, to a variously substituted cyclopentadiene.



The first approach was used in the synthesis of dithia, epoxyimino and methyleneimino analogues of PGH.

The key stage in the synthesis of the dithia analogues (XCIIa–c) of PGH is the formation of a disulphide bridge in the appropriate 9,11-dimercapto substituted prostanoids (XCIa–d).[71–73]



(XCI a–d) OH(THP,Ac) (XCII a–c)

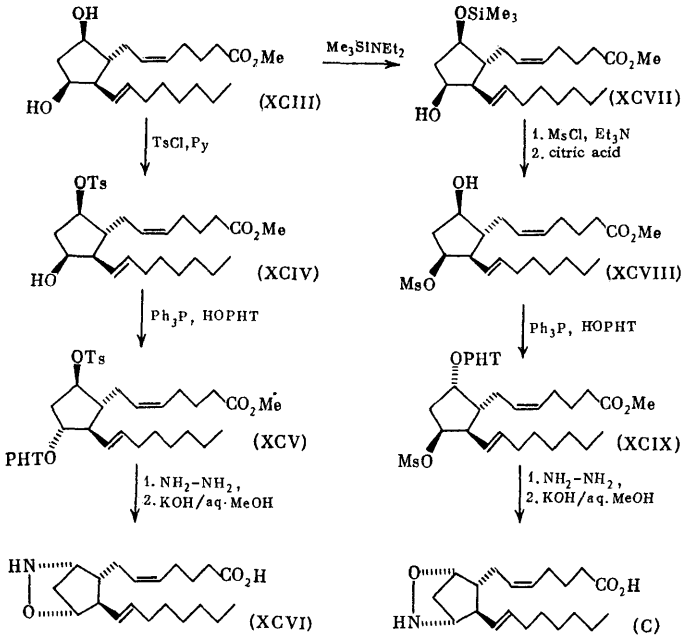
a) $R^1 = CO_2Me$, $X—Y = CH\overset{E}{=}CH$

b) $R^1 = CO_2Me$, $X—Y = C\equiv C$

c) $R^1 = CH_2OAc$, $X—Y = C\equiv C$

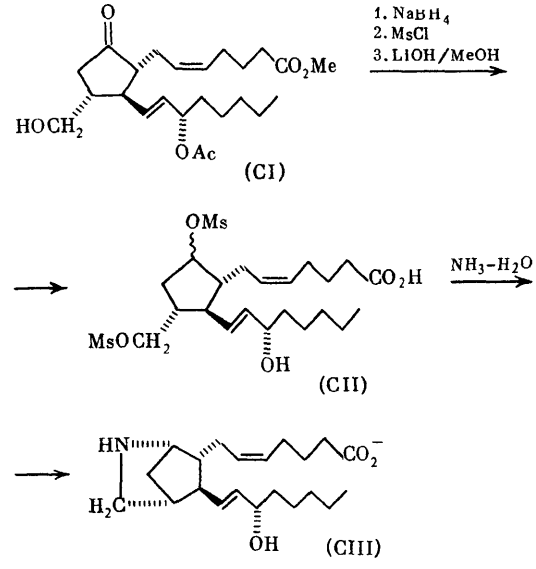
(XCI)	R^1	X–Y	R	Reagent
a	CO_2Me	$CH\overset{E}{=}CH$	H	MnO_2
b			Me	O_2, MeONa/MeOH
c	CO_2Me	$C\equiv C$	Ac	K_2CO_3/MeOH
d	CH_2OAc			

The regioisomeric 9,11-epoxyimino analogues (XCVI) and (C) were obtained from 15-deoxy-11β-$PGF_{2\beta}$ (XCIII).[74] The regioselective tosylation of the less screened 9-hydroxyl group in 11β-$PGF_{2\beta}$ leads to the derivative (XCIV). Subsequently on treatment with triphenylphosphine, *N*-hydroxyphthalimide and diethyl azodicarboxylate compound (XCIV) gave the *N*-alkoxyphthalimide (XCV) from which the epoxyimine (XCVI) was formed on removing the phthalimide protection. In a similar manner the selective trimethylsilyl protection of the 9-hydroxy function of 11β=$PGF_{2\beta}$ leads to the derivative (XCVII). Mesylation of the C(11) alcohol group and removal of silyl protection gives compound (XCVIII) from which the regioisomeric epoxyimine (C) is formed through the alkoxyphthalimide (XCIX).



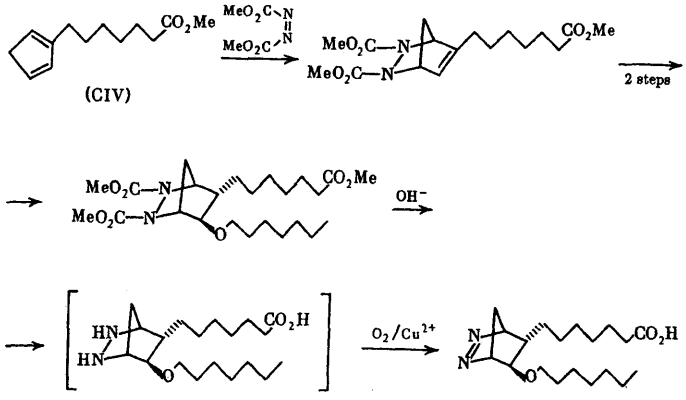
PHT = phthalimido

The methylenimino analogue (CIII) was obtained from the 11-hydroxymethylprostanoid (CI).[75] Reduction of the 9-keto group in the latter and mesylation of the resulting diol leads to the bismesylate (CII), which on reaction with 40% aqueous ammonia gives the ammonium salt of methyleneimino-15-deoxy-PGH_2 (CIII).



A second approach was used in the synthesis of 9,11-azo analogues of the cyclic endoperoxides. The cyclic system of the latter was formed by the Diels–Alder addition of dimethyl(diethyl) azodicarboxylate to a substituted cyclopentadiene of type (CIV). Forming the bridge with the azo group was effected by the alkaline hydrolysis of both methoxycarbonyl(ethoxycarbonyl) groups of the

bicycle and then direct air oxidation of the intermediate hydrazine derivatives in the presence of a divalent copper salt.[76]



VI. Heteroanalogues of prostacyclin

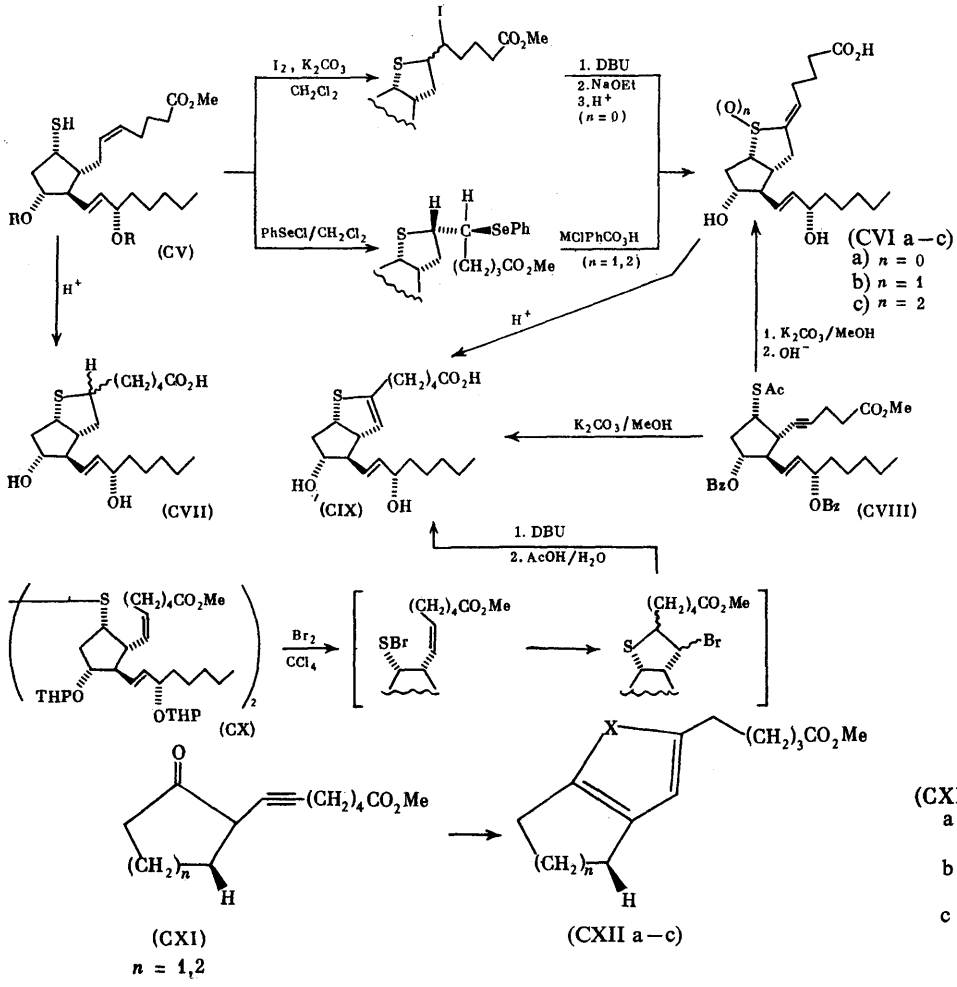
Heteroprostacyclins are described in the literature with heteroatoms at the most varied positions of the molecule. Among those appearing in publications in the last decade it is possible to name 3-oxa,[77–82] 3-aza(thia),[79] 4-thia,[83] 5-aza,[84] 11-oxa,[85] 11-thia,[86] 12-aza,[87] 13-oxa(thia),[88–90] 13-aza[91] and *o*-phenylene analogues.[81,92]

The methods of synthesising such prostacyclin analogues are no different in principle from the methods of forming the basic skeleton of the heteroprostanoids considered above and the synthesis of the *cis*-enol ether system in them is effected by classical means. Consequently in the present review only the modification of the heteroatom of the enol ether fragment is examined. The main purpose of the modification is the replacement of the chemically and metabolically unstable enol ether group by biologically equivalent and/or isosteric structures which are more stable and may have promising use in medicine.

The formation of an enol ether modified with a heteroatom in such heterocyclic PGI analogues was effected using mainly three approaches.

1. Formation of the heterocycle with the participation of the activated multiple bond of the α-chain.

This method is widely used when constructing the enol ether system of natural prostacyclin. Applying it to the 9-mercapto-5,6-*trans* derivatives of $PGF_{2\alpha}$ (CV) leads to the 9-thiaprostacyclins (CVIa–c), (CVII).[93,94] The analogue (CVIa) is also formed by intramolecular attack of the thioacetate grouping at the triple bond in the derivative (CVIII).[95]



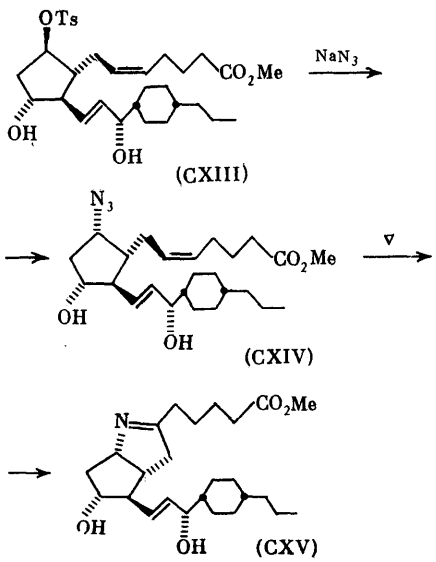
(CXII)

	Reagent	X	n
a	H_2S/HCl	S	1,2
	$PhNH_2$,	PhN	1,2
b	$Py{\cdot}HCl_2$		
	$Hg(O_2CCF_3)_2$	–	–
c	Ac_2O,	O	2
	p-TsOH		

The 9-thiaprostacyclin (CIX) was obtained from the disulphide (CX).[96] In this case cyclisation occurs as a result of attack by the Δ^6-double bond at the activated sulphenyl bromide grouping. The same analogue was obtained on cyclisation of the thioacetate (CVIII) by the action of potassium carbonate in methanol,[97] and also on treatment of the 9-thiaprostacyclin (CVIa) with acid.[98]

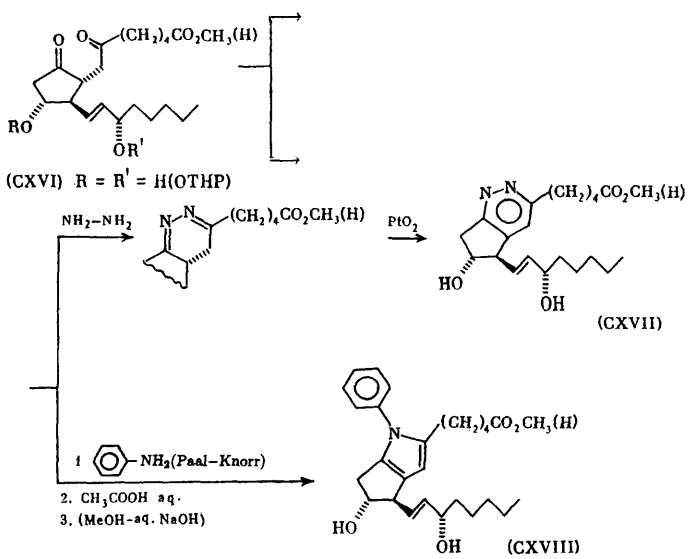
The simplest thiophene (CXIIa), pyrrole (CXIIb) and furan (CXIIc) analogues of prostacyclin were synthesised from the readily accessible 4-alkynylketones (CXI).[99]

The 9-azaprostacyclin (CXV) was obtained using as the key stage the pyrolysis of the azide (CXIV) formed from the tosylate (CXIII).[100]

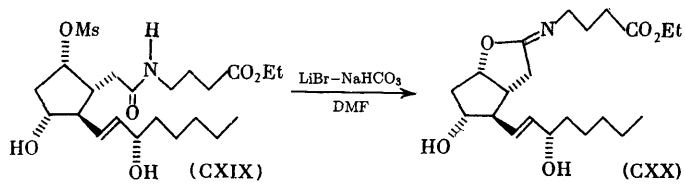


2. Formation of the heterocycle with the participation of other functional groups of the α-chain.

Construction of the heterocyclic systems of the pyridazoprostacyclin (CXVII) and the pyrrole analogue (CXVIII) was effected from the 1,4-dicarbonyl system of 6-keto-PGF_1 (CXVI).[101,102]

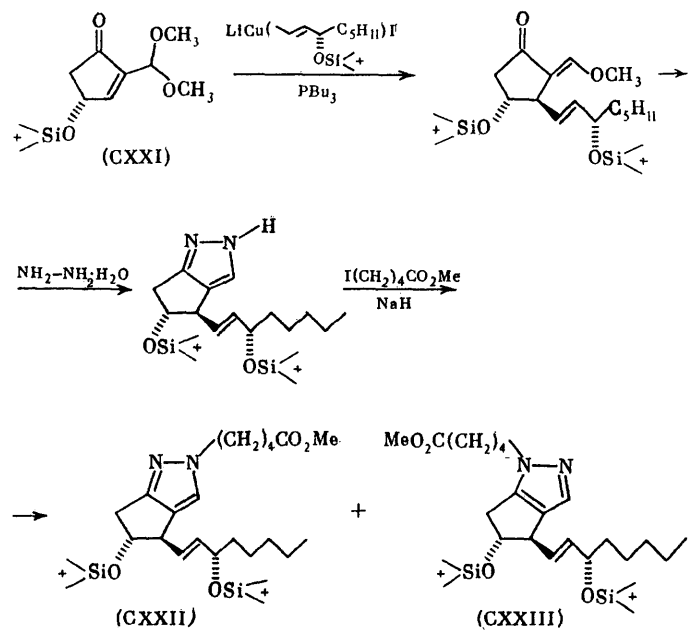


The 5-azaprostacyclin (CXX) was obtained by the cyclisation of the 9-mesyl derivative of the 5-aza-6-ketoprostanoid (CXIX) with a mixture of lithium bromide and sodium hydrogen carbonate.[103]

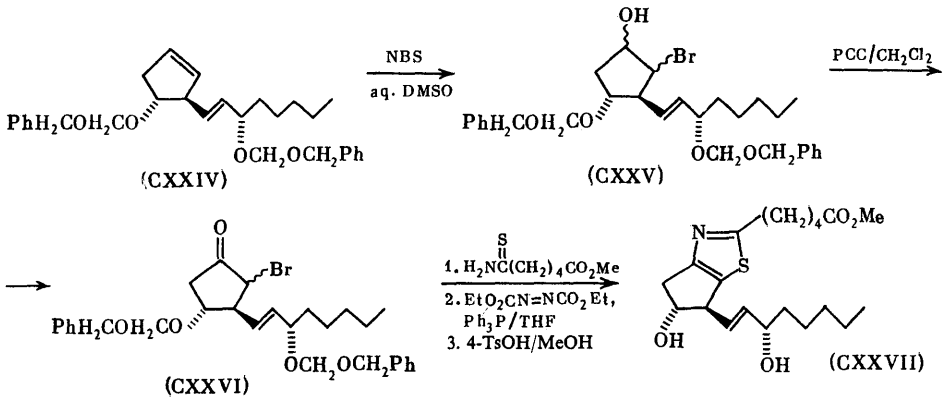


3. Formation of the heterocycle from functionalised derivatives of cyclopentane.

The synthesis of the pyrazole analogues (CXXII) and (CXXIII) from the precursor (CXXI) belongs to this group of schemes.[104]

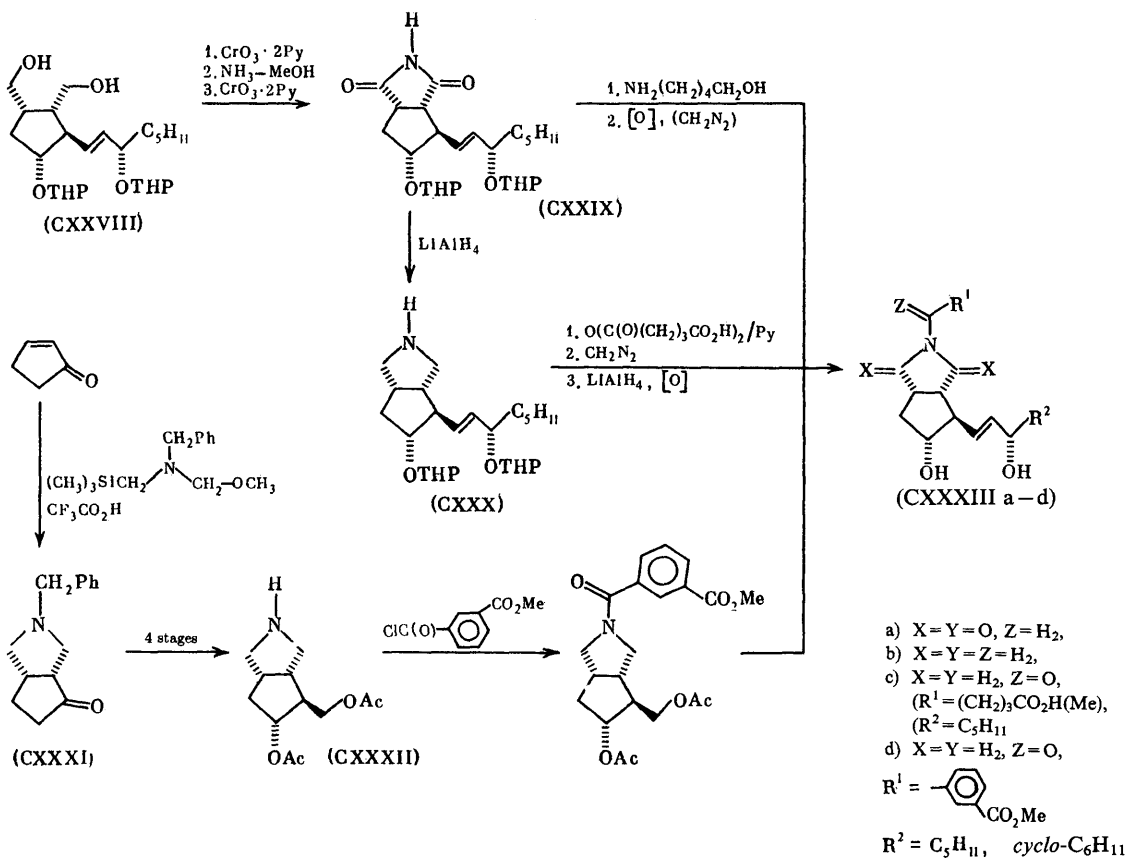


The regiospecific formation of the bromohydrin (CXXV) takes place by the reaction of *N*-bromosuccinimide with compound (CXXIV). Oxidation of the bromohydrin leads to the formation of the bromoketone (CXXVI) which is converted into the thiazolylprostacyclin (CXXVII) by reaction with adipic acid thioamide and subsequent dehydration.[105,106]

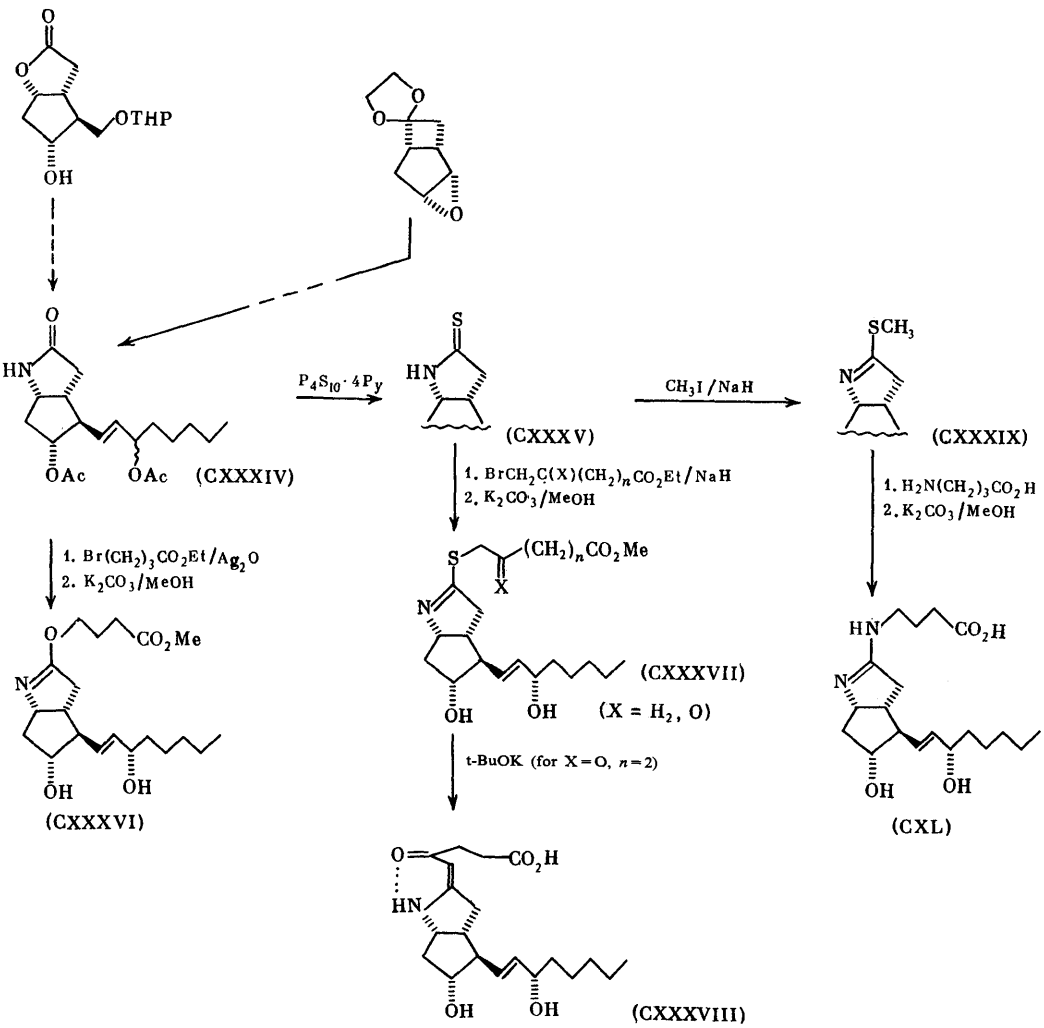


The 6-aza analogues (CXXXIIIa–d) were synthesised by the alkylation (acylation) of the succinimide precursor (CXXIX) [formed from the diol (CXXVIII) in three stages] or from its reduction product (CXXX) and also from the bicyclic diacetate (CXXXII) obtained from the ketone (CXXXI).[107,108]

The β-heteroiminoprostacyclins (CXXXVI)–(CXXXVIII) and (CXL) were synthesised from the lactam (CXXXIV) which may be obtained from the Corey lactone or from the ethylene ketal of 2,3-epoxybicyclo[3.2.0]heptan-6-one. On reaction with the Lawesson reagent the lactam (CXXXIV) was converted into the thiolactam (CXXXV). Alkylation of compounds (CXXXIV) and (CXXXV) leads to the analogues (CXXXVI) and (CXXXVII). The further transformation of compound (CXXXVII) leads to



4-keto-9-deoxy-9-aza-PGI_2 (CXXXVIII). Ammonolysis of compound (CXXXIX) with γ-aminobutyric acid gives the amidine (CXL).[109,110]



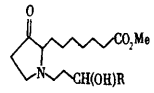
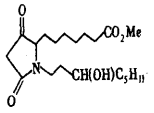
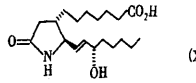
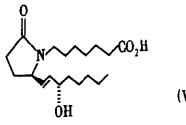
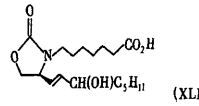
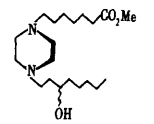
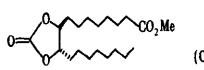
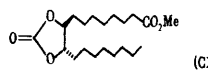
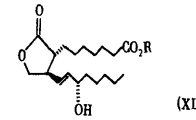
VII. Biological activity of heteroprostanoids

Among the numerous data in the literature on the biological activity of PG heteroanalogues we will discuss chiefly those which refer to the modification of the natural structure affecting the biological properties in a favourable manner, i.e. increasing any form of activity (narrowing the spectrum of action) or increasing the metabolic stability of the compound (prolonging its therapeutic effect).

The biological actions of prostaglandins can be divided into several main types. 1. The effect on the vascular and non-vascular smooth musculature, the contracting or relaxing activity. 2. The gastroprotective effect, including the regulation of secretion of gastric juice both as a result of a change in tone of the smooth muscle tissue and of the effect of PG on water and electrolyte transport in them. 3. The hormonotropic action, including the regulation of gland function by internal secretion stimulating the synthesis of hormones. One of the most important forms of biological activity of PG belongs to this direction, viz. the luteolytic effect, the action on the reproductive system through the regulation of ovarian function. 4. The pro- or anti-inflammatory action. The anti-inflammatory effect is probably linked with the inhibition of natural PG biosynthesis. 5. The induction and inhibition of platelet aggregation. 6. The anti-PG effect of synthetic prostanoids consists of a weakening of the effect of natural PG. The synthetic analogue is, as a rule, an antagonist of the appropriate receptor for the natural PG.

It is assumed that PG acts as a complex with the cell receptor of a given organ on an adenylate cyclase system, increasing or reducing its activity and thereby changing the rate of conversion of ATP into adenosine 3′,5′-phosphate, i.e. changing the content of c-AMP in the tissues of an organ. Consequently PG-like activity is assessed according to the ability to bind to a receptor or according to the change in c-AMP content and a comparison is made with the dose of natural PG equivalent in effect. Tests are used to assess the metabolic stability of a prostanoid which measure the affinity for enzymes responsible for metabolism (15-hydroxy-PG-dehydrogenase, Δ^{13}-PG-reductase, etc.). The anti-PG effect, linked with the action on the process of biosynthesis of prostaglandins from arachidonic acid, is displayed in the ability to inhibit the enzymes of PG biosynthesis (PG-synthetase, PG-isomerase).

Table 4. Types of biological action of the heteroprostanoids.

Heteroprostanoids	Biological action	Active concentration g ml^{-1}	Reference
	Contraction of rat uterus muscle	$0\times5-1\times10^{-7}$	[27]
 PGE$_1$	Ditto	5×10^{-7} 1×10^{-9}	[129]
 (XL) PGF$_{2\alpha}$	Contraction of trachea	4×10^{-6} 4×10^{-7}	[32]
 (VI)	Bronchdilator	1×10^{-6}	[4]
 (XLII)	»	5×10^{-5}	[33]
PGE$_2$ 	Increase of tone of smooth muscle organs Ditto Strengthening of spasmogenic reactions caused by PGE$_2$ Reduction of rat arterial pressure	10^{-9} $10^{-5}-10^{-6}$ $10^{-6}-10^{-7}$ $0\times5-1\times10^{-3}$	[151]
 (CXLI)	Weakening of activity on trachea	$4\times10^{-6}-5\times10^{-4}$	[36]
 (CXLII) PGE	Ditto	$5\times10^{-4}-2.5\times10^{-3}$	
 (XLIII)	Effect on smooth muscle	10^{-8}	[111, 112]

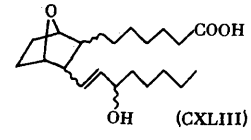
1. Effect on vascular and non-vascular smooth muscle. Gastroprotective, hormonal and pro- or anti-inflammatory activity of heteroprostanoids

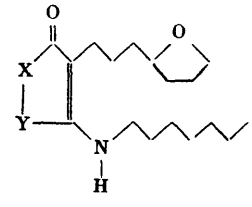
Many synthetic heteroprostanoids show activity on smooth muscle characteristic of PG. However both the size and the sign of the effect depend on the form of the target tissue, which is the specificity of a given prostanoid (Table 4). For example, the 11-aza analogues (XL) do not display a contractive activity on guinea pig and rat ileum but contract the trachea like PGE_2 and also cause rhythmic venous contraction.[32]

The 9,11-dioxa analogues (CXLI) and (CXLII) display strong relaxant activity.[36] The range of active concentrations of these analogues in relaxing the trachea is 0.004 – 2.5 mg ml^{-1}, i.e. they are approximately 100 times more potent than the natural PGs. The given compounds do not exert a relaxant effect on bronchospasm, they do not affect blood pressure and do not cause intestinal disorders (in contrast to PGE_2) in tests *in vivo*. The 10-oxa-11-deoxy analogues (XLIII) are patented as stimulants in certain species, they may be used in gastro-intestinal disorders and are non-toxic.[111]

A link can be traced between structure and activity of the synthetic heteroprostanoids. The methyl esters of the 10-oxa-11-deoxy-PGE analogues are inactive in the interruption of pregnancy,[112] and the acids of the 11-deoxy-E_1 and E_2 series have moderate contracting activity at concentrations of 10^{-7} g ml^{-1} and low toxicity.[34,113] The 11-methyl derivatives of this series inhibit the secretion of gastric juice in dogs and possess anti-hypertensive activity.[114]

The configuration of substituents at the chiral centres of the molecule affect the biological activity even more appreciably. In the 10-oxa-9,9-dicarba analogues of PGH_1 (CXLIII), which possess vasocontracting and broncho-stimulating activity in many tests *in vitro*, the configuration at C(8, 12,15) has a significant effect.[115,116] Thus the 15β-hydroxy derivatives are most active towards the stimulation of the vascular and respiratory musculature and in the case of the 8-isoconfiguration this effect is strengthened. The contracting activity is appreciably reduced in the 15α-hydroxy derivative and in the case of the natural 8,12,15-configuration. a vasodilatation is observed. These same principles are observed in experiments *in vitro* on trachea and smooth muscle. The 11-oxa-13-azaprostanoid (CXLIVa) at a dose of 10 mg kg^{-1} displays a marked antiadrenergic effect (70% relative to control) and also restores the frequency of cardiac contractions and normalises impaired atrioventricular conduction in the adrenaline arrhythmia model in guinea pigs. Compounds (CXLIVb, c) display an antioedemic effect in the carrageenan inflammation model in the rat.[13]


(CXLIII)


a) X = CH_2, Y = O; b) X = O, Y = $CH(CH_3)$; c) X = $CH(CH_3)$, Y = O.

(CXLIVa – c)

Bronchodilating activity is characteristic of numerous derivatives of 3-, 5- and 16-oxa analogues of PGE and PGF. The 3-*O*-hetero analogues have been patented as antiasthmatics,[117] and the 13-thiaprostanoids of the E_1 and E_2 series as hypotensive agents.[46]

A comparative assessment has been carried out of the activity of several synthetic aza and thia analogues in their ability to bind to PG receptors of the appropriate tissues or in the size of the change in c-AMP concentration (Table 5).[23,63] As is seen from the table a hundredfold concentration of the 11,12-seco-aza analogue (CXLV) is necessary for the display of activity comparable to PGE_1. Compound (CXLVI) was the most active among the 8-aza analogues but it was ten times less potent than PGE_1. The most potent of the tested series, the 11,12-seco analogue (CXLVII), was five times less potent than PGE_1 and comparable with tetrahydro-PGA_2 in stimulating c-AMP, although both PGE_1 and tetrahydro-PGA_2 bound more strongly to the receptor of lipocytes than (CXLVII). However on detailed investigation of the biological properties of (CXLVII) it was shown[65] that the compound is not a substrate of 15-hydroxy-PG-dehydrogenase and therefore has enhanced metabolic stability. Furthermore it was established in tests *in vivo* that the analogue (CXLVII) has a higher specificity of action, it is inactive in relation to gastric secretion and is not an antihypertensive agent.

Table 5. Comparative assessment of the activity of synthetic heteroanalogues of the prostaglandins.[23,63,65]

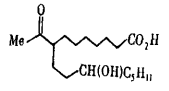
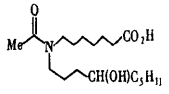
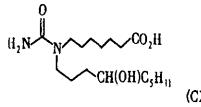
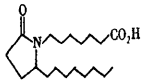
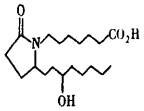
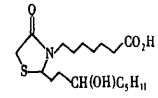
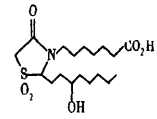
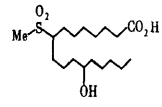
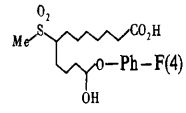
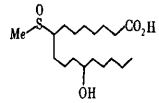
Compound *	c-AMP concentration, mg ml^{-1}				Binding to lipocyte receptor, relative to PGE_1
	1.0	10	25	10^3	
PGE_1	54	60	62	62	1
Dihydro-PGE_1	10	25	26	—	—
Tetrahydro-PGA_1	10	25	26	—	10
	2	11	14	23	833
	—	10	17	17	—
 (CXLV)	2	23	43	40	—
 (XXVIa)	0.7	—	8	13	8300
 (XXVIb)	0.9	—	8	18	4600

Table 5 (contd.).

Compound *	c-AMP concentration, mg ml^{-1}				Binding to lipocyte receptor, relative to PGE_1
	1.0	10	25	10^3	
	1.4	—	8	25	390
 (CXLVI)	5.2	—	27	37	60
 (CXLVII)	14	—	27	38	670
	1	—	23	27	1110
	4	—	40	57	7140

*Activity of PGE_1 at *c*-AMP concentration 10^{-2} mg ml^{-1} was 8, at *c*-AMP 10^{-1} it was 25. Activity of (CXLVII) at 10^{-1} mg ml^{-1} was 2.

The 15α-isomer of (+)-7-oxa-$PGF_{1\alpha}$ (CXLVIII) at a concentration of 100 μg mol^{-1} displays 10% activity of PGE_1 in stimulating adenylate cyclase and has 5% activity of $PGF_{1\alpha}$ in stimulating smooth muscle.[118] The 15β-isomer at a concentration of 1 μg ml^{-1} inhibits the action of $PGF_{1\alpha}$ at a concentration of 250 ng ml^{-1}.

The 9,11-dideoxy (CXLIX) and 9,11,15-trideoxy (CL) derivatives of 7-oxa-PG are antagonists of the action of PGE_1 and $PGF_{1\alpha}$ on smooth muscle.[119] These examples demonstrate the effect on activity of the number of hydroxyl groups and their configuration at C(15). The inhibitory activity is reduced as the degree of hydroxylation of the compound increases.

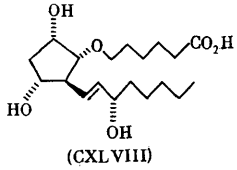
The 7-thia-$PGF_{1\alpha}$ analogue (CLI) shows 10% activity of $PGF_{1\alpha}$ in the extent of binding to the corpus luteum receptor and stimulates adenylate cyclase while its 9β-, 11β-, 8β- and 12α-isomers with unnatural chirality display only 1% of the activity of the analogue with the natural configuration.[120] The 9,11,15-trideoxy-7-thia derivative (CLII) is an inhibitor of contractions and an inhibitor of adenylate cyclase. The values of I_{50} of 15 μM for (CLII) and 5 μM for (CLI) in the inhibition of placenta PG-15-dehydrogenase show that these compounds also regulate the concentration of the natural PG *in vivo*.[120] The relatively little studied group of 9- and

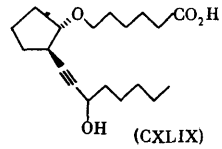
11-oxa-PG analogues which showed 0.05–0.005 of the activity of PGE_2 [121,122] and the 11-thia analogues[123] must be regarded as promising biologically active heteroanalogues.

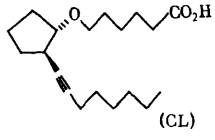
The 10-oxaseco analogue (CLIII) shows high efficiency (approximately equal to the activity of PGE_2 and 30% of that of PGE_1) in the inhibition of gastric juice secretion.[68] The same activity was displayed by the 10,12-diaza analogues of PGE.[124] The 16-phenoxy-PGs proved to be good therapeutic preparations for the treatment of various lesions of the gastro-intestinal tract.[125,126] In preliminary tests the 7,13-dithia analogues of groups E, F and D displayed antiulcer activity without side effects.[49]

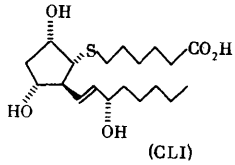
A luteotropic effect among the heteroanalogues of PG was detected only for the 5- and 16-oxa analogues[127,128] although compounds more potent and selective than PGF_2 were discovered amongst them.

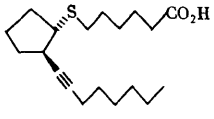
As already mentioned, an inflammatory effect is characteristic of the natural PGs. At the same time certain heteroanalogues display clearly marked anti-inflammatory activity. Thus the 12-aza analogue of PGE (CLIV) is similar in activity to hydrocortisone.[129] The 9,11-dithia analogue (CLV) [36] is nine times more potent than aspirin and is a potential nonsteroidal anti-inflammatory agent. This compound is an inhibitor of PG-synthetase on which apparently the anti-inflammatory effect is based. Anti-inflammatory activity is also possessed by the 9,11-dioxa analogues.[36] A series of heteroanalogues of endoperoxides has been patented as anti-inflammatory agents.[130]

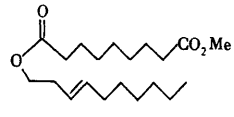

(CXLVIII)

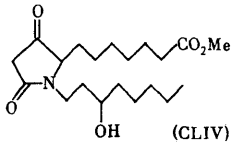

(CXLIX)

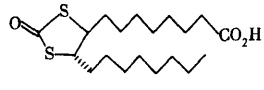

(CL)


(CLI)


(CLII)


(CLIII)


(CLIV)

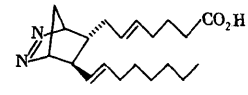

(CLV)

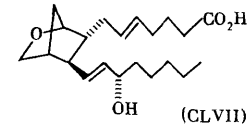
2. The induction and inhibition of platelet aggregation by heteroanalogues of endoperoxides, prostacyclins and PGE

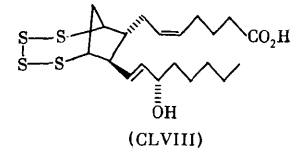
After discovering the fact that the endoperoxides have a significantly stronger effect on the respiratory and vascular smooth muscle than PGE_2 and PGF, the attention of investigators was turned to these unstable intermediate products of the biosynthesis of the primary PGs. Interest in this was strengthened when the ability of endoperoxides to induce rapid and irreversible aggregation of platelets (an action uncharacteristic of the primary PGs) was discovered[131] and it was established that the endoperoxides are metabolised to prostacyclin (PGI_2) and thromboxane A_2 (TxA_2) which are opposite to one another in their action. Prostacyclin is an inhibitor of platelet aggregation and relaxes smooth muscle. Thromboxane A_2, like PGH_2 and PGG_2, is produced in the process of platelet aggregation, but is far more active in inducing aggregation and as an inhibitor of PGE_1-stimulated c-AMP. The extreme instability of these three intermediate prostaglandins, their high potency and reputed role in the biological action of PGs caused the interest in the synthesis of more stable analogues, including heteroanalogues, which might serve as models for studying the mechanism of PG action.

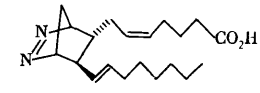
The 9,11-diaza analogues of the endoperoxide (CLVI), like PGG_2, cause a rapid and irreversible platelet aggregation at concentrations of $10^{-5}-10^{-6}$ M. They are almost eight times more potent than PGG_2, seven times more potent than PGH_2, are metabolically more stable and are also 1500 times more potent than PGE_2 in contracting smooth muscle.[132]

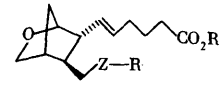
The epoxymethano analogue (CLVII) is an efficient broncho-constricting agent, it is 3–7 times more potent than PGG_2, but less potent in platelet aggregation.[133,134] The 9,11-dithia-PGH_2 analogue (XCIIb) [71,72] is very potent in contraction of the aorta (24 × PGH_2 and 5000 × PGE_2) and is an inducer of platelet aggregation. The endotetrasulphide PHG_2 analogue (CLVIII) causes platelet aggregation in spite of the presence in the structure of the bulky S-containing group which however does not hinder the binding with the endoperoxide receptor.[3] On the other hand the heteroanalogues of PGH_2 without a 15-hydroxy grouping (XCVI), (C) and (CLIX) display inhibitory activity in relation to thromboxane A_2 synthetase and are antagonists of platelet aggregation induced by PGH_2 or by arachidonic acid.[74,135,136] Endoperoxides of such structure have been patented as anti-inflammatory and antithrombotic agents.[137] The epoxymethano (CLX) and the carba analogues of PGH_2 with a heteroatom at position 14 proved to be inhibitors of platelet aggregation.[138]

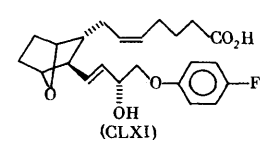

(CLVI)


(CLVII)


(CLVIII)


(CLIX)


(CLX) Z = O, NH


(CLXI)

The oxabicyclo[2.2.1]heptane prostanoids with natural α- and ω-chains are known as potential analogues of thromboxanes. Their analogue (CLXI), containing a 16-fluorophenoxy fragment in the

ω-chain, has high TxA_2-like activity and at a concentration of 4×10^{-11} M is 100 times more potent than the standard agonist, viz. 9,11-epoxymethano-PGH_2.[139] The 12β-isomer is the most active among the isomers with the natural configuration. In the absence of a hydroxyl function from the ω-chain these prostanoids display the opposite activity. Thus the alkyl thioethers of 7-oxabicyclo-[2.2.1]heptane (CLXII) are antagonists of the thromboxane receptor.[53] They possess inhibitory activity towards TxA_2 synthetase and are 30–40 times more potent than ethanol in inhibiting platelet aggregation. The amidocarbamates, amides and diamides of 7-oxabicycloheptanes have also been patented as inhibitors of platelet aggregation.[140] The recently synthesised sulphonamido derivatives of bicycloheptane prostanoids (CLXIII) are also antagonists of the thromboxane receptor.[57,60]

The diametrically opposite biological action of PGI_2 to the action of TxA_2 and the endoperoxides PGH_2 and PGG_2 in platelet aggregation forms a basis to affirm that the balance between the activities of these two groups of arachidonic acid metabolites determines thrombosis and haemostasis. However, in spite of the large number of studies on the biochemistry and physiology of PGI_2 there is still no definite theory on the mechanism of its action. It was shown that like PGE prostacyclin increases the concentration of c-AMP in blood.[141,142] The increase in the c-AMP level, as proposed, must inhibit hydrolysis of arachidonic acid phospholipid ester and thereby moderate the release of arachidonic acid and its metabolism to endoperoxide.

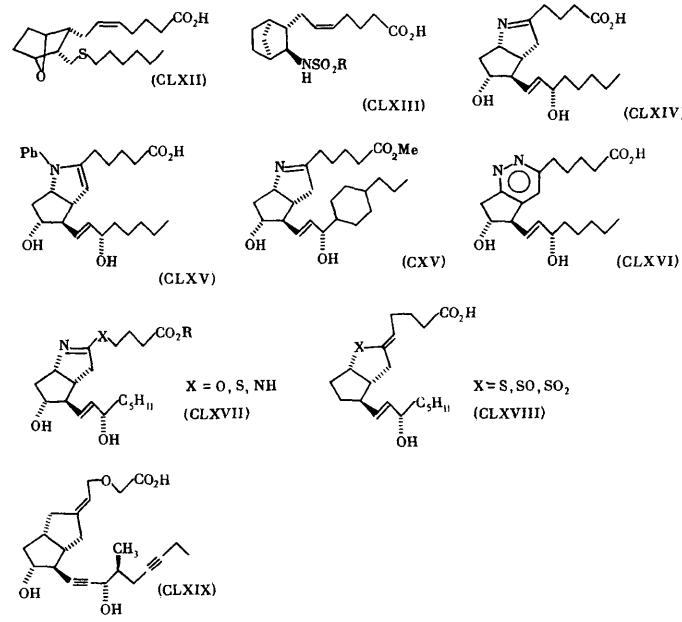
The synthesis of stable analogues of prostacyclin is an urgent problem. Since the instability of PGI_2 is linked primarily with the presence of the enol ether fragment and the carboxyl function near to it, the synthesis of analogues of PGI in which the oxygen of the ring was replaced by nitrogen or sulphur has been effected.

The prostacyclin analogues (CLXIV) and (CLXV) are equivalent to PGI_2 in activity although compound (CLXIV) in contrast to PGI_2 inhibits the synthesis of leucotrienes.[102,143,144] The promise of the recently synthesised azaheteroprostacyclin OP-2507 (CXV) as an anticerebral ischaemic agent is linked with the antithromboxane activity displayed by it.[100] The 6-aza analogues of PGI obtained recently display weak activity.[108] It is considered that among the stable analogues of prostacyclin the greatest activity is possessed by analogues with a sp^2-hybridised atom at C(6), for example compounds (CLXVI)–(CLXVIII).[101] Furthermore the stereochemistry of the upper chain at the Δ^5-double bond affects the activity. The most active proved to be the configuration with a *trans* orientation of the heteroatom and the hydrogen atom at C(5).[93,94,145]

Further modification of the enol ether fragment was effected by the synthesis of 4-keto-9-deoxy-9-aza-PGI analogues.[110]

The potency of these compounds as inhibitors of ADP-induced platelet aggregation was less than a quarter of that of PGE_1 and was 0.01 of the potency of PGI_2. The similarity of the ^1H NMR parameters of this group of compounds and of prostacyclin indicates significant conformational similarity but seemingly, due to the rigidity of the vinyl amide system, the carboxyl group is prevented from reaching the binding centre of the PGI_2 receptor.

The thia analogues are less potent than PGI_2 and the aza-analogues[71,131,132] in platelet aggregation and in contrast to PGI_2 possess vasocontracting activity. It was noted that the inhibitory activity was reduced from the 6,9-thia analogues to the 6,9-sulpho analogues.[93,94]



The most promising among the prostacyclins proved to be its carba analogue, iloprost, consequently synthetic efforts are directed to the further modification of iloprost. In the prostacyclin series, as for PGE, it was discovered that the introduction of a heteroatom into position 3 increases the metabolic stability of a compound[78–80,146,147] since in this case the first metabolic process is blocked, viz. the oxidation in the β-position relative to the carboxyl group.[79] The potency of compounds is reduced at the same time but this is compensated successfully by modification of the lower chain, particularly by introducing alkyl fragments into the ω-chain. The stable and five times more potent 3-oxaprostacyclin (CLXIX) was thus obtained.[78]

In addition to the prostacyclins, 8-aza-11-desoxy-PGE_1,[148] 10-aza analogues,[37] 12-aza-PGE analogues[129] and 9,11-diaza analogues[29] display inhibitory activity in platelet aggregation. The 3-oxa-4,5,6-trinor-3,7-*m*-phenylene analogue of PGE_1 is 30 times more active than PGE in inhibiting platelet aggregation. Anti-aggregatory activity is possessed by azacyclic analogues of the primary PG derivatives, viz. pyrazolidine- and piperazinediones,[18] hydantoin and imidazole derivatives.[28–30]

The reduction in the activity of isomers having an unnatural configuration at the chiral centres 8 and 15 is explained[18,30,116] by the important role of the configuration of the α-chain and the 15-hydroxyl group in anti-aggregatory activity. It must be affirmed that anti-aggregatory activity is observed for the analogues of primary PG identical in configuration to the natural PGs.

13-Azaprostanoic acid (13-APA) possesses unique anti-aggregatory activity and at a concentration of 10^{-5} M is a specific inhibitor of platelet aggregation induced by arachidonic acid, PGH_2 and its epoxymethane analogue.[42,149]

At the same time 13-APA does not inhibit aggregation induced by ADP or thrombin. In a detailed experimental investigation of this unique specificity of 13-APA it was established that 13-APA does not inhibit aggregation by the production of c-AMP, as is assumed for prostacyclin and PGE_1, which in contrast to it are not so

selective in the inhibition of platelet aggregation. Furthermore it was established experimentally that 13-APA is not an antagonist of the action of PGI_2 and PGE_1, since they, although not stimulating adenyl cyclase, do not interfere with the production of c-AMP. In the arachidonic cascade (the metabolic pathway for AA) three places have been proposed at which inhibition of platelet aggregation by 13-APA may occur. There are 1) inhibition of cyclo-oxygenase (PG-synthetase) which transforms AA into the endoperoxide. This action is similar to the action of the non-steroidal anti-inflammatory agents aspirin and indomethacin. 2) Inhibition of thromboxane synthetase and the consequent blocking of the transformation of PGH_2 to TxA_2 like the action of imidazole and the aza analogues of endoperoxide (XCVI), (C) and (CLIX).[74,135,136] 3) Direct inhibition of the thromboxane–endoperoxide receptor. It was established experimentally that 13-APA does not inhibit either the synthesis of endoperoxide or the synthesis of thromboxane but possibly selectively blocks the reaction of TxA_2 and PGH_2 with the platelet receptor. This hypothesis is confirmed by the structural similarity of 13-APA with the unstable PGs, which are active in aggregation, and the sensitivity of the inhibiting activity to molecular and stereochemical modification.[149] When analysing the data on the antiprostaglandin activity and the inhibitory capabilities of the heteroprostanoids it is possible to separate certain structural elements responsible for the development of these properties. Thus the absence of a 15-hydroxyl function is necessary[150] for the development of antagonistic activity or, when discussing isomers, an unnatural configuration for the 15-hydroxyl function.[118–120] The inhibitory action of a compound is also seemingly linked to a significant degree with the absence of a 15-hydroxyl group i.e. anti-inflammatory action,[36,137] inhibition of biosynthesis,[71,74,135,136,150] inhibition of the effect of the natural PGs [29,119] and the inhibition of platelet aggregation.[28,149,150] It has already been mentioned that inhibitory activity is reduced with an increase in the extent of hydroxylation of a compound.[119] From the fairly few examples available it may be suggested that the replacement of the 9,11-carbon atoms by a heteroatom or blocking the free hydroxyl functions in these positions in combination with the absence of a 15-hydroxyl group, will give a compound with anti-inflammatory or other antagonistic activity.[36,74,135,137]

When explaining the appearance of PG-like activity or the activities of PGH_2 and PGI_2 considerable importance is attached to the conformity of the stereochemical configuration of a modified PG to the configuration of the natural PGs.[30,116,118] This applies to any modification of the PG molecule including modification by a heteroatom. To increase metabolic stability it is expedient to modify that part of the molecule which is subject to change in the metabolic process. Seemingly a decisive role in all cases is played by retaining a qualitative similarity between an analogue and the natural PG which itself will be closest to the PG receptor of a cell.

After preparation of the manuscript for publication several publications have appeared on the theme of the review.[152–170]

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