ANALOGUES OF PROSTACYCLIN (PGI_2) MODIFIED IN THE 2-OXABICYCLO[3.3.0]OCTANE FRAGMENT* (REVIEW)

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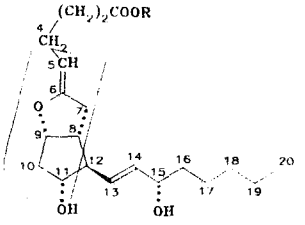
A review is given of the synthetic analogs of the prostacyclins having greater chemical and metabolic stability than prostacyclin itself. Possible routes for synthesis are discussed.

Prostacyclin [synonyms: prostaglandin X (PGX), prostaglandin I_2 (PGI_2), and 6,9α-epoxy-9-deoxyprostaglandin $F_{2\alpha}$] was discovered in 1976 [1]. This compound immediately caused great interest, since it possessed the highest activity known at that time against the aggregation of thrombocytes [2, 3]. The chemical structure of prostaglandin (1) was established by a group of scientists under the direction of Johnson [4] in the same year, 1976. Immediately after this, total chemical synthesis of this compound were performed independently in various scientific centers of the world. The great interest of synthetic chemists in this problem is shown by the fact that during the first seven months six different methods of obtaining PGI_2 were reported [5-10].



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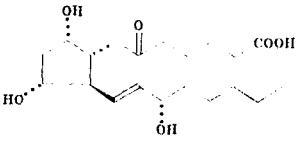

2

In biological tests PGI_2 is usually employed in the form of the readily water-soluble sodium salt (1; R = Na). However, the probability of the development of medicinal preparations based on PGI_2 remains extremely low, since the period of decomposition of aqueous solutions of prostacyclin in the organism in 3-4 min [11, 12] (or, according to [13, 14], ~10 min). This characteristic of substances of the type (1) is due mainly to the hydrolytic lability of the enol ether grouping of PGI_2. As a result of this reaction, both *in vitro* and *in vivo*, prostacyclin (I) always forms the same decomposition product – 6-ketoprostaglandin $F_{1\alpha}$ (2) [14, 15]. Consequently, soon after the discovery of PGI_2 searches were begun for analogs of it that would be distinguished by an increased chemical and metabolic stability [16] with the retention of a high antithrombic activity that would be free from some side effects of prostacyclin [17, 18].

A number of structural changes in the PGI_2 molecule could, a priori, impart to it an increased resistance to the action of the universal enzymes catabolizing all prostanoids (prostaglandin 13, 14-hydrogenase and prostaglandin 15-dehydrogenase, and also enzyme systems causing the β-oxidation of hydrocarbon residues). Such changes would include substitution at the $C_{(13)}$, $C_{(14)}$, $C_{(15)}$, $C_{(16)}$, $C_{(2)}$, and $C_{(3)}$ atoms, and, to a certain extent, also at the $C_{(17)}$, $C_{(12)}$, and $C_{(4)}$ atoms. It is important to emphasize that the methods of synthesizing these atoms of PGI_2 differ little from the methods of obtaining their prototype.

*This review is an expanded version of the plenary lecture of the authors at the 3rd All-Union Conference on Synthetic and Applied Studies of Prostaglandins [in Russian], Ufa (1984).

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The subject of the present review is a consideration of modified prostacyclins having the C—O bond of the bicyclic system stabilized in some way, and also prostacyclins the reactivity of which depends more on other structural fragments of the molecule than on the O—C=C chain of atoms. We shall therefore consider only those compounds in which the changes involve the $C_{(8)}$-$C_{(12)}$ and O atoms of the tetrahydrofuran ring of the initial prostanoid, the hydrogen atoms at $C_{(8)}$, $C_{(9)}$, and $C_{(10)}$, and the chemical bonds of the bicyclic system. The replacement of the $C_{(8)}$—$C_{(9)}$ double bond by an ordinary bond will be considered if it takes place as a consequence of the migration of Δ^8 or is accompanied by a supplementary modification of other centers of the molecule. Change in the bonds of the $C_{(4)}$ atom will be reflected in individual cases — when, a priori, they should have a substantial influence on the chemical properties of the O—C=C structural fragment. On the basis of what has been said above, the chemically significant region of structural modification of prostacyclin is outlined in formula (1).

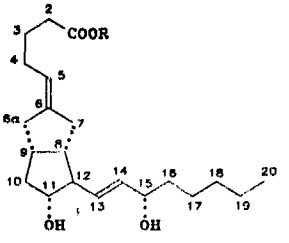
In the preparation of this report, we have also used reviews published previously [16, 19, 22]; we assume that they succeeded in fully reflecting the situation with respect to prostacyclin analogues up to and including 1984.

THE MOST IMPORTANT SYNTHETIC ANALOGUES OF PGI_2. SUBSTITUTION OF ATOMS IN POSITIONS 5-11

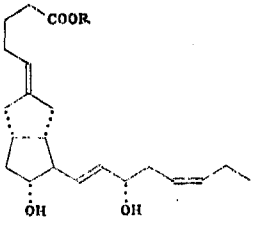
Let us first consider PGI_2 analogues in which the oxygen atom has been replaced by a methylene group — so-called carbaprostacyclins. The first representative of them — 6α-carbaprostacyclin I_2 (3) [it has also been called carbacyclin, 6,9α-methanoprostaglandin I_2, 6α-carbacyclin, and 9(0)-methanoprostacyclin] — was obtained in 1978.

At the end of the 70s, the interest of synthetic chemists in the preparation of PGI_2 analogues containued to be very high: In the course of ten months, one and the same compound (3) was obtained independently in six scientific centers [23-31]; for later work, see [32-36]. Below we also consider other carbacyclins (4-12).*

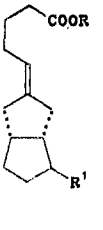
Carbacyclin (3) is characterized as a compound that is completely stable to hydrolysis *in vitro* under conditions modeling physiological conditions [23, 27-31]; however, it has proved to be as unstable metabolically as natural PGI_2 [41]. Further modification of carbacyclin by the introduction of fluorine atoms into the periphery of the molecule were obviously undertaken with the aim of increasing the life of the carbacyclins *in vivo*, as well, (compounds (6) and (7)). Unfortunately, there is still no information on their activity and metabolic stability.



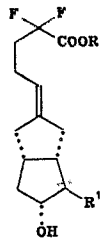
3 R=CH_3, H, Na



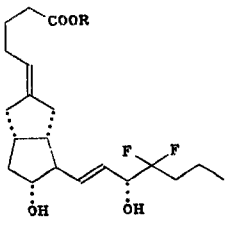
4 [37]



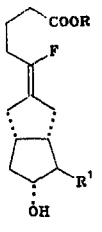
5 [38]



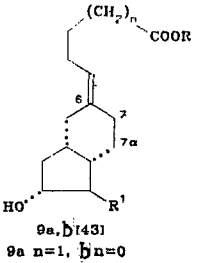
6 [39]



7 [40]

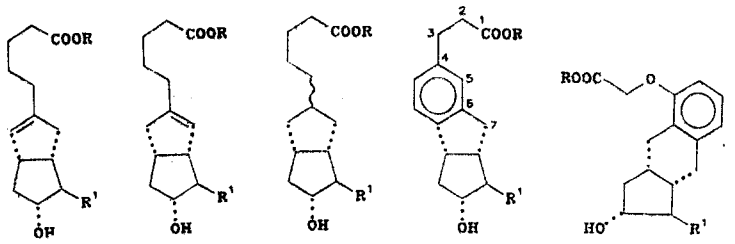


8 [42]



9a,b [43]
9a n=1, b n=0

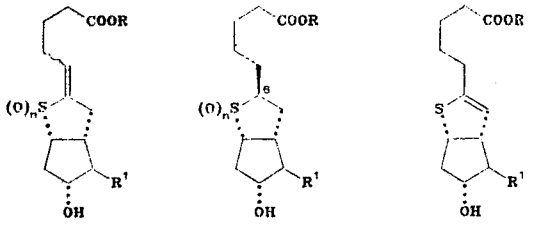
*Here and below in the formulas the substituent attached to the five-membered ring R^1 = 3(S)-hydroxyoct-1(E)-enyl.



10 [44] 11 [45] 12 [46] 13 [47] 14 [13]

Carbacyclins (4), (5), (8), and also (10-12) were synthesized as close structural analogues of the prototype (3). Compounds (9a, b), (13), and (14), are already extremely remote analogues of PGI_2; for example, in the cyclopentanoindane (13), the α-chain of a prostanoid has been only formally replaced by a fragment with the same number of carbon–carbon bonds.

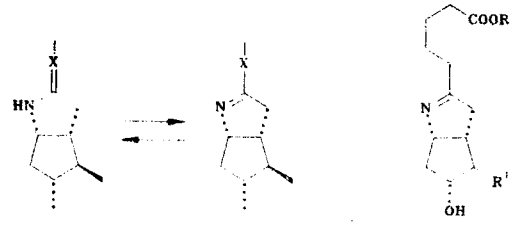
Thiaprostaglandin I_2 (15) was synthesized in 1977. This compound, and its analogues (16-20), including some with a hydrogenated $C_{(5)}$—$C_{(6)}$ bond, are still the only modified prostacyclins in which the heteroatom can have different degrees of oxidation; furthermore, each of the 9(0)-sulfoxa derivatives can exist in two epimeric forms, depending on the configuration of the sulfoxide bond. The thiaprostacyclin (15) is completely stable in a neutral medium and can be purified chromatographically on silica gel. This compound also possesses antiaggregation properties and its action is more prolonged than that of PGI_2 [49].



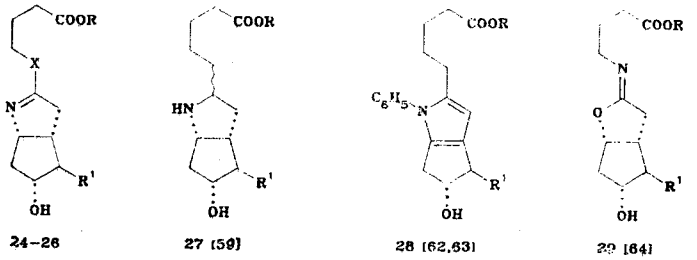
15-17 18-20 21 [57,58]

15 [49—54], 18 [52, 56] n=0; 16 [50, 51, 55], 19 [56] n=1; 17 [50, 55], 20 [56] n=2

For the **9(0)-aza analogues of PGI_2** the problem of their structure is complicated further by the fact that the five-membered heterocycle can exist in the enamine (22a) or the imine (22b) forms. Nevertheless, in the papers known to us only structure (22b) is found.



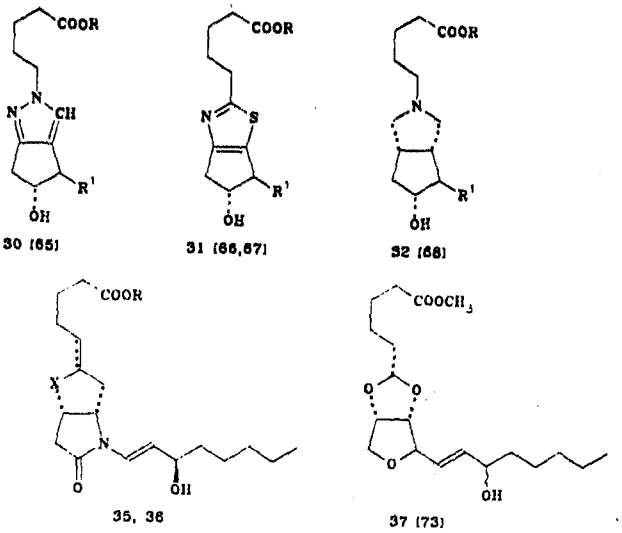
22a 22b 23 [59]



24-26 27 [59] 28 [62,63] 29 [64]

24 X=O, 25 X=S, 26 X=NR [16, 60, 61]

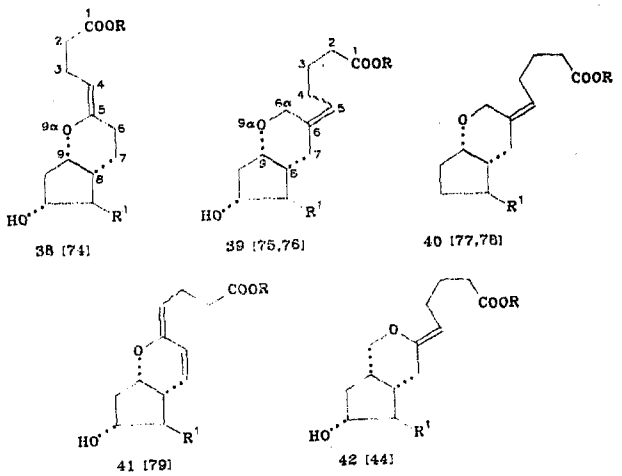
We may also mention compounds (30-37) in which two substitutions of atoms in the bicyclic systems have now been made. These substances are only superficially similar to the prostacyclins and, disregarding the principle of the construction of the octenol chain, the methods for their production likewise differ from those customary in prostaglandin chemistry.



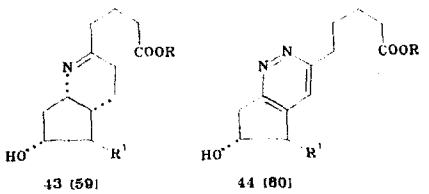
The aza analogues of the prostacyclins are more stable than PGI_2 [60, 61]. Thus, the stability of the ethyl ester of 5-aza-PGI_2 (29: R = C_2H_5) is higher than that of the methyl ester of PGI_2 (1, R = CH_3): It can be stored for several months at 4°C and the half-decomposition time of its aqueous solutions at pH 7 is 33 h, while the PGI_2 ester at the physiological pH is stable for only 4.5-6 h [12, 64].

HOMOPROSTACYCLINS AND THEIR HETEROANALOGUES

Some remote analogues of PGI_2 with a six-membered ring in the place of one of the five-membered rings in the bicyclic fragment have been mentioned above [compounds (9a, b) and (14)]. There are three types of "true" homoprostacyclins: with an additional methylene group between $C_{(6)}$ and $C_{(7)}$ or the $C_{(6)}$ and 9α (the ethereal oxygen atom) atoms or between the $C_{(9)}$ and 9α atoms [compounds (38-42)].

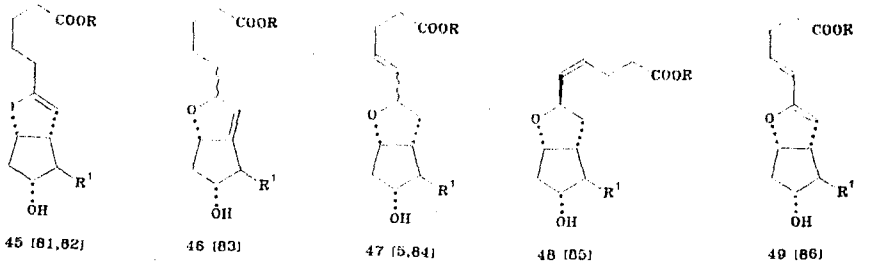


This group of compounds also contains the 2-nor-7-homo-9(O)-azaprostacyclin derivative (43) and the 6,9-pyridazaprostacyclins (44). Analogues (39) and (40) do not contain the enol ether structural fragment and are therefore more resistant to hydrolysis than PGI_2. The pyridazines (44) are unstable in an alkaline medium, and with m-chloroperbenzoic acid they each form two N-oxides the stability of which is considerably higher than that of the initial compounds. They are stable in a neutral medium and possess interesting biological properties [38].

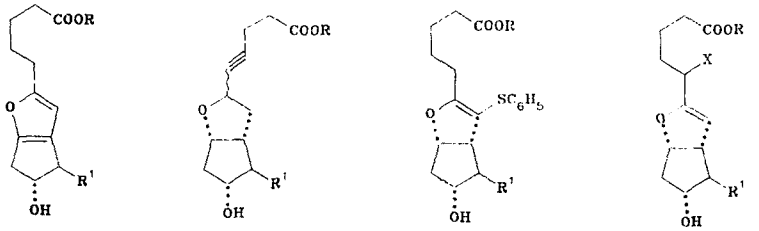


DIHYDROPROSTACYCLINS I_1

This name unites all those prostacyclin analogues in which the double carbon–carbon bond has been eliminated from the $C_{(5)}$—$C_{(6)}$ position. Such analogues may also contain another C=C bond or a triple bond in place of the double bond [compounds of types (45)-(51)].



45 [81,82] 46 [83] 47 [5,84] 48 [85] 49 [86]



50 [87] 51 [85] 52 [88-90] 53-58

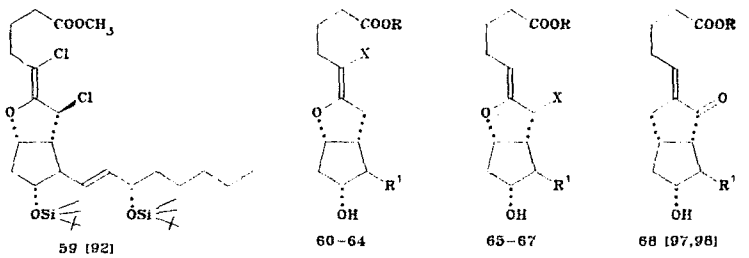
53 [89, 90] X=β-SC_6H_5; 54 [89, 90] X=β-$S(O)C_6H_5$; 55 [91] X=F; 56 [93] X=O, 57 [91, 92] X=Br; 58 [91, 92] X=Cl

The 5- and 7-substituted prostanoids (52-58) are also known, their prototype being compound (45). These substances are frequently formed during the synthesis of the 5- or 7-substituted PGI_2's.

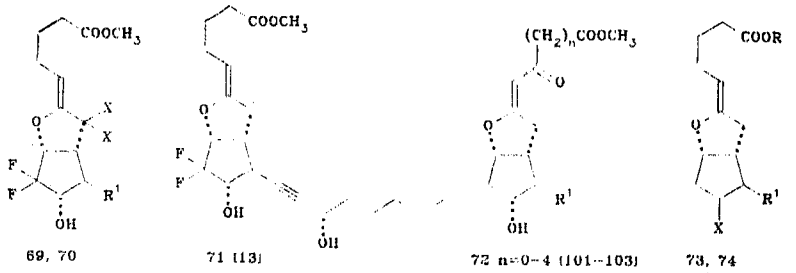
Each of the analogues (45), (49), and (52-58) contains an enol ether grouping. There is very little information on the hydrolytic stability of these compounds, concrete results having been published only in relation to the analogue (52): Its biological activity is retained under extremely severe conditions (pH 1.5, room temperature) for 1 h [88]. In the other cases the authors state merely that the enol ether fragment can be subjected to hydrolysis but the stability of the substances synthesized is higher than that of PGI_2 [61, 86, 93].

PROSTAGLANDINS I_2 SUBSTITUTED IN THE BICYCLIC FRAGMENT OR AT $C_{(5)}$ $C_{(4)}$

The rate-determining stage of the hydrolysis of the enol ether group is its attack by a H_3O^+ ion [94, 95], and therefore any electron-accepting substituents adjacent to this group should stabilize the molecule. We may mention first the PGI_2 analogues (59-72), containing electronegative systems in the $C_{(7)}$, $C_{(8)}$, $C_{(5)}$, and $C_{(4)}$ positions.



59 [92] 60-64 65-67 68 [97,98]



69, 70 71 [13] 72 n=0-4 [101-103] 73, 74

60 [82] X=CN; 61 [91, 107], 67 [90], 70 [98], 74 [105] X=F; 62 [91] X=Cl; 63 [88, 90] X=SC_6H_5; 64 [88] X=$S(O)C_6H_5$; 65 [89, 90] X=β-OH; 66 [89, 90] X=β-$OOCCH_3$; 69 [20, 99], 73 [104] X=H

The fluorinated analogue (74) contains the modifying atom in a position too remote for it to be possible to expect an effect of it on the hydrolytic stability of the compounds in relation to the O—C=C— fragment.

A series of amide derivatives of compound (61) is also known [106].

The stabilities of compounds (59)-(72) are substantially higher than that of their prototype PGI_2. The half-decomposition period of 5(E)-chloro-PGI_2 (62) at pH 4.7 is 1.5 h, and that of the 5(Z)-analogue under the same conditions is 8 h [92]. It can be seen that an important role is also played by the spatial position of the substituents at the $C_{(5)}=C_{(6)}$ bond. For comparison: The half-decomposition period of PGI_2 at pH 5.98 is 22.4 seconds, and at pH 7.46 it is 10.5 min [14]. A phenylthio substituent has an even greater stabilizing effect: for (63) $\tau_{1/2}$ = 1.5 days (pH 7.4) [70], or 1 day at pH 1.5 [88]. A distinct stabilizing effect is also exerted by electron-repelling groups in position 7 of the prostacyclin system. The period of half-decomposition of compound (65) at pH 4.7 is 3 h and that of the 7-fluoro analogue (67) is 2.5 days [90]. Thanks to their stability, compounds (65) and (66) can be purified by column chromatography on silica gel [89]. A special effect is exerted by the 7-oxo group: In buffer solutions at pH 6.7 and 10.7 the prostacyclin analogue (68) does not change in 26 days, and even at pH 2 the $\tau_{1/2}$ value for this substance is 4 days [98]. However, its antiaggregation activity is 15 times smaller than that of natural PGI_2.

Studies of stability by chemical methods and by biotesting have been described in detail using the prostacyclin (71) as an example in [13]. Thus, if a solution of the sodium salt of this compound is subjected successively to acidification, extraction, and chemical modification, i.e., the procedure that normally precedes many methods for the qualitative determination of the prostanoids, the bulk of (71) remains unchanged, while natural PGI_2 decomposes completely. The half-decomposition periods of the prostacyclins (71) and PGI_2 have been measured by the biotesting of solutions (10^{-8} M) in bicarbonate buffers (pH 7.4) at 37°C. A lowering of the bioresponse by 50% was observed for solutions of (71) after 24 h, and for PGI_2 after only 10 min [14].

Consequently, in order to find the optimum of the indices for the creation of a sufficiently effective medical preparation — for example, an antithrombic drug — a compromise must be found between the usually lower (by an order of magnitude and more) antithrombic activity of PGI_2 analogues and the substantially higher hydrolytic stability of these compounds as compared with natural prostacyclin.

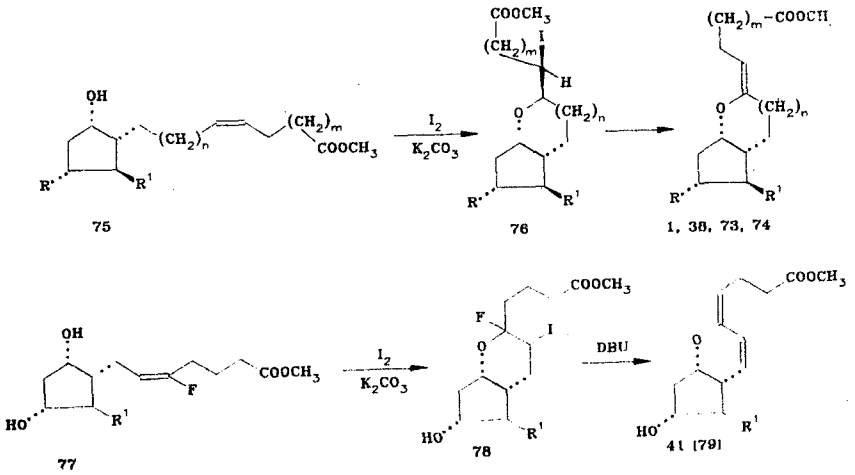
SOME FEATURES OF THE SYNTHESIS OF UNNATURAL PGI_2 ANALOGUES

At the present time, a large amount of material has accumulated on methods of synthesizing prostacyclins. In the present review, we are able to dwell only on some of the, in our view, most important principles of obtaining the desired compounds. We shall first consider methods common for the synthesis of the most diverse groups of PGI_2 analogues.

Nucleophilic Cyclization of $PGF_{2\alpha}$ Derivatives

These include, as a rule, those methods of cyclization in which the actual closure of the furan ring of the prostacyclin system is initiated by the action of a positively polarized halogen atom or other grouping. This has led to the term "iodocyclization reaction"; it is just this reaction that we used in the first syntheses of PGI_2 and PGI_3 [82, 107]. A number of substituted prostacyclins having two five-membered rings condensed in the usual manner [20, 99, 100, 104, 105, 108, 109], two types of homoprostacyclins (scheme I), and the tetrahydroprostacyclin (50) [87] have been obtained.

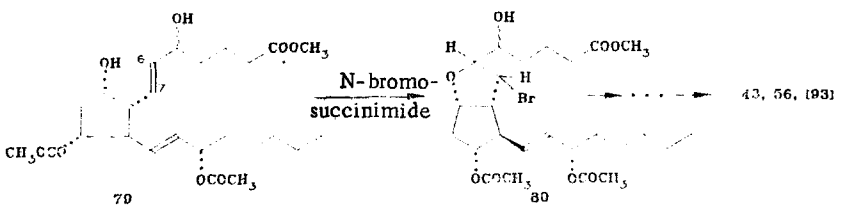
Scheme 1



1 R=OH, n=0, m=2 [82, 106]; 38 R=OH, n=1, m=1 [74]; 73 R=H, n=0, m=2 [104]; 74 R=F, n=0, m=2 [105]; DBU=1,8-diazobicyclo[5.4.0]undec-7-ene

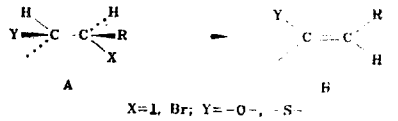
The reaction is usually initiated either by molecular iodine in the presence of carbonate or by compounds containing a positively polarized bromine atom [5, 92]. The addition of a 9α-hydroxy (or thiol, see below) group to the C=C double bond of the side chain takes place in such a way that the oxygen (or sulfur) atom always attacks the $C_{(6)}$ atom, forming a new five-membered heterocycle. This takes place correctly even in those cases where the double bond in the initial prostaglandin has shifted into the $C_{(6)}$—$C_{(7)}$ position (scheme 2) [57]. An exception is formed by cases of the heterocyclization of the methyl ester of 5-fluoro-$PGF_{2\alpha}$ (scheme 1) in which the $C_{(5)}$ atom proves to be the most electrophilic, and a case in which the formation of the furan ring is impossible in principle (scheme 1, n = 1).

Scheme 2



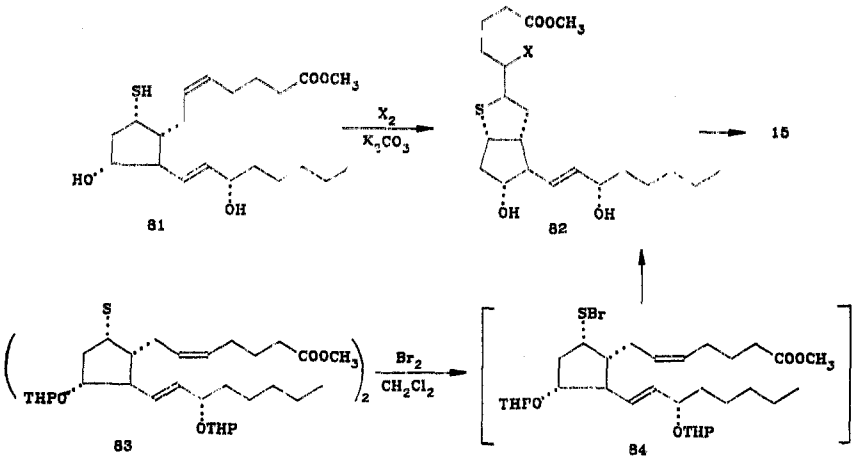
In parallel with the 6β-substituted precursors of PGI_2 (scheme 1, variants with n = 0 and 2), the corresponding **6α-epimers** are also formed, and these, on dehydrohalogenation, give Δ^4-dehydroprostacyclin I_1 (type (47)) [22]. The key stage of the formation of the enol ether or enethiol ether function in all cases is the trans-elimination of a hydrogen halide from the adduct A (scheme 3). The stereochemical conditions necessary for this are usually fulfilled in the case of the β-arrangement of the 6-substituent in the cyclization product (scheme 1).

Scheme 3



The halocyclization reaction can also be extended to the synthesis of the thiaprostacyclins (15) (scheme 4). In this case, the primary formation is assumed of the structural fragment (81) in which the closure of the tetrahydrothiophene ring then takes place [49, 51]. Since the same thiaprostacyclin can be synthesized from the disulfide (83) (see scheme 4) [52, 57], the hypothesis of the formation of an intermediate sulfenyl halide appears logical.

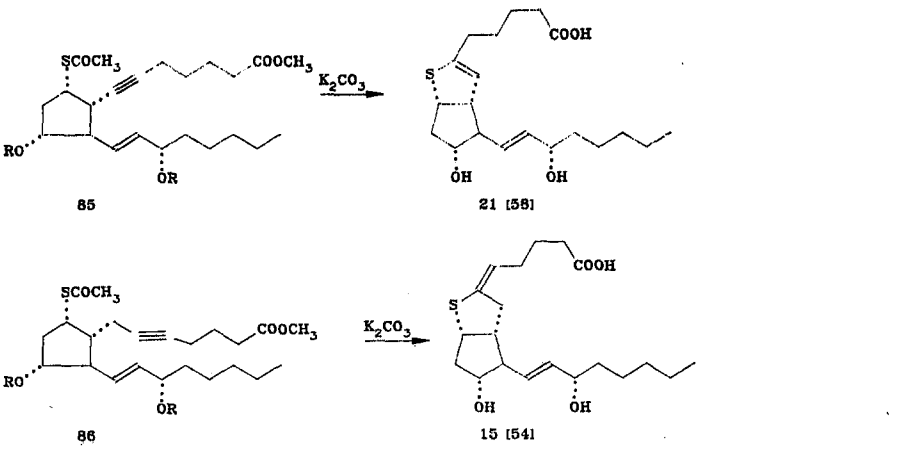
Scheme 4



X = I, Br; here and below, THP = tetrahydropyran-2-yl

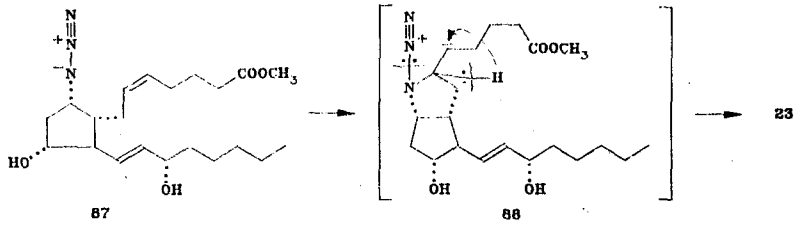
The thiol group proves to be so reactive that, for example, 9(0)-thia-5,6-dihydro-PGI_2 (18) is formed under the conditions of simple acid catalysis [56]. The 4E- and 4Z-isomers of 9-thio- and 9-acethylthio-$PGF_{2\alpha}$ also cyclize in the presence of phenylselenyl chloride with the formation of the 6-epimers of type (18) compounds containing phenylselenyl groups in position 5 [50, 55].

Scheme 5



The nucleophilic cyclization of thiaprostaglandin derivatives containing a triple bond in the α-chain deserves special attention. Both in this case and in the cyclization of the corresponding 9-oxa prototype [110], it is just the five-membered heterocycle that is formed (scheme 5).

Scheme 6

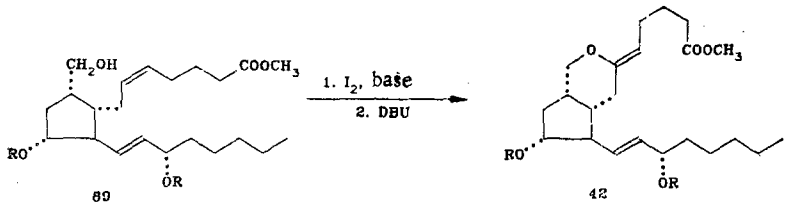


The production of 9-aza-PGI_2 (23) [59] also falls within the general scheme of synthesizing PGI_2 analogues by the nucleophilic heterocyclization method if the formation of the pyrrolidine ring is regarded as a consequence of an attack on the $C_{(6)}$ atom of the α-chain of the initial prostanoid by the negative end of the dipole of the azide fragment followed by the elimination of a molecule of nitrogen (scheme 6).

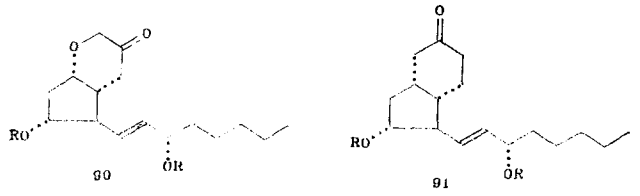
Methods of Synthesizing Homoprostacyclins

We have already mentioned some syntheses of these compounds (scheme 1). A homoprostacyclin derivative [(42), scheme 7], used for the synthesis of the carbacyclin (10), has also been obtained by the iodocyclization method [44].

Scheme 7

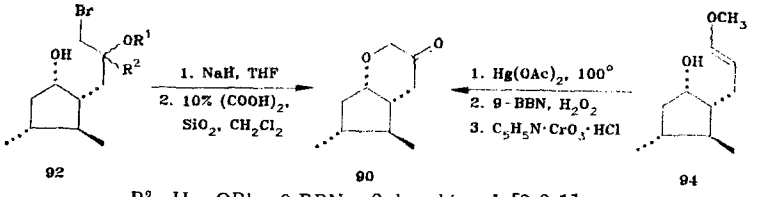


In the synthesis of 6,9α-methanoepoxyprostaglandins $F_{2\alpha}$ (39) or 6,9α-methano-7α-homoprostaglandin I_2 (9) the same principle is used as in the synthesis of many carbacyclins (see below): First, bicyclic ketones are constructed — in the present case (90) and (91) with the preformed ω-chains of the prostanoid — and from these the desired homoprostacyclins are obtained by the traditional method using the Wittig reaction.



The 2-oxabicyclo[4.3.0]nonan-4-one system (90) was synthesized by cyclization with the participation of the α-hydroxy group of the initial cyclopentanol and the thermal nucleophilic atom of a vicinal α-propyl [75, 77, 78] or α-propenyl [76] substituent (scheme 8).

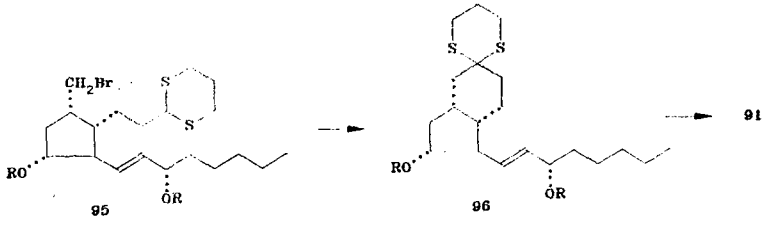
Scheme 8



R^2=H, OR^1; 9-BBN= 9-borabicyclo[3,3,1]nonane

Scheme 9 shows the synthesis of the bicyclo[4,3,0]nonan-3-one system (91). It makes use of a comparatively rare method of alkylating a thioacetal carbon atom in the presence of lithium diisopropylamide [43].

Scheme 9

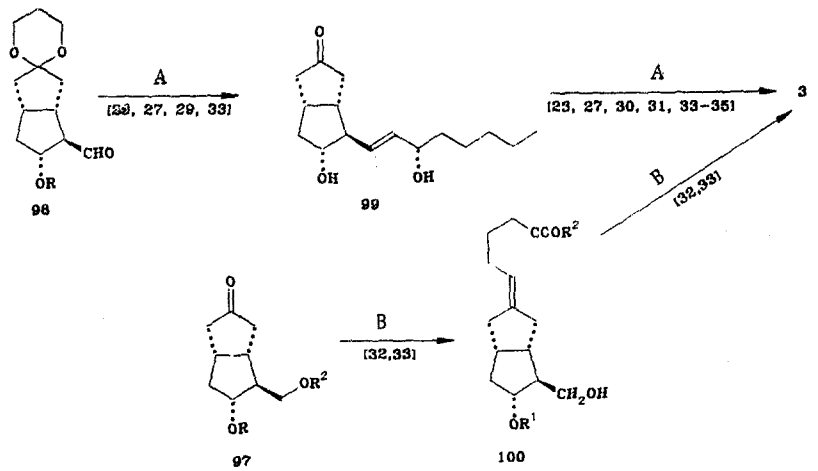


Methods of Synthesizing 9(O)-Carbaprostacyclin I_2 and Its Analogues

The multiplicity of approaches to the synthesis of carbacyclins known at the present time was developed with the aim of obtaining the prototype of this series of prostanoids — 9(O)-methanoprostacyclin (3) itself. As a rule, the key stage is the preparation of the bicyclo-[3.3.0]octan-3-one synthons (97)-(99), onto the molecules of which are built the hydrocarbon chains of a prostanoid in one sequence or the other (scheme 10, routes A and B). The majority

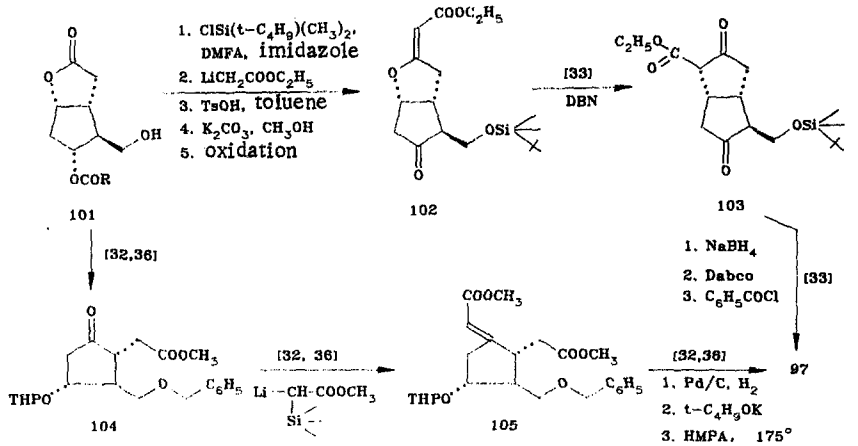
of authors, however, prefer to synthesize carbacyclins by route A, and the originality of each new method of obtaining compounds of type (3) resides mainly just in the stage of forming the intermediates — the synthons (97)-(99).

Scheme 10



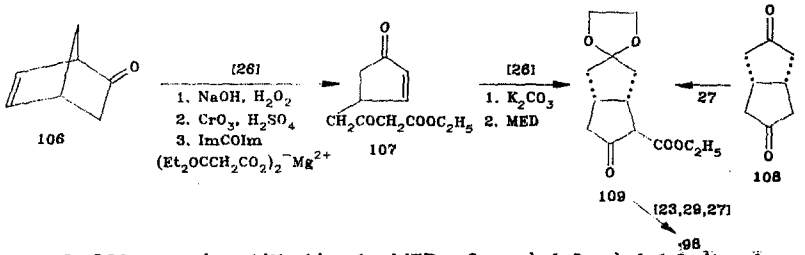
Schemes 11 and 12 show examples of the synthesis of the key synthons (97) and (98), and scheme (13) the four main routes to the synthesis of synthon (99).

Scheme 11



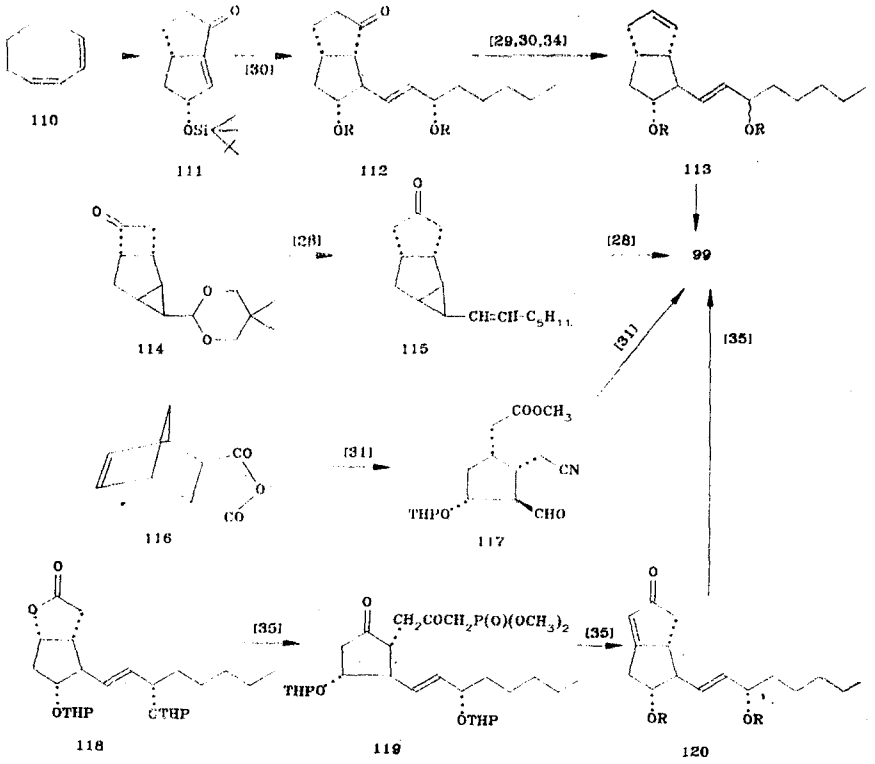
DBN = 1,5-diazabicyclo[4,3,0]non-5-ene; Dabco = 1,4-diazabicyclo[2,2,2]octane, HMPA = = hexamethylphosphoramide

Scheme 12

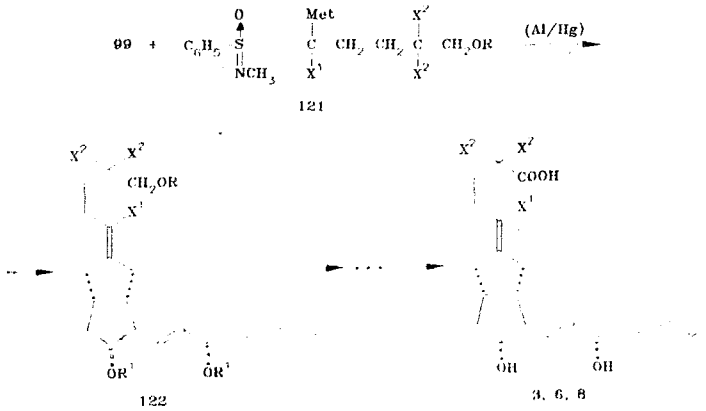


ImCOIm = carbonyldiimidazole; MED = 2-methyl-2-ethyl-1,3-dioxolane

Scheme 13



Scheme 14

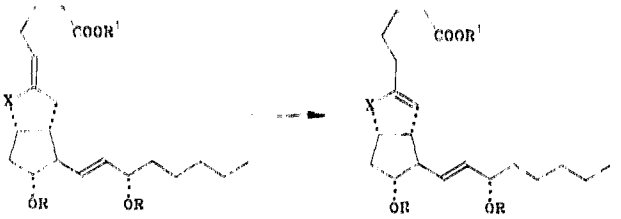


3 $X^1=X^2=H$ (Met=MgBr); 6 $X^1=H$, $X^2=F$ (Met=MgBr); 8 $X^1=F$, $X^2=H$ (Met=Li)

According to scheme 9 (route A), the concluding stage in the majority of syntheses is the Wittig reaction with the introduction of a carboxybutenyl residue. However, another heteroorganic synthesis, based on sulfoximides, is also used (scheme 14). Not only carbacyclin (3) [28] but also its 5-fluoro analogue (8) [42] and its 2,2-difluoro analogue (6) [39] have been obtained by this method.

MODIFICATION OF DERIVATIVES OF PGI_2 AND OF ITS Δ^6-ISOMER

The simplest method of synthesizing other prostacyclins from PGI_2 or its 9(O)-thia analogues is the isomerization of the Δ^5-bond, which takes place in methanol, in the presence of an acid catalyst. During rearrangement, the molecule of prostacyclin (1) adds the elements of methanol and the $C_{(5)}$—$C_{(6)}$ bond, but in the following stage (thermolysis) these are eliminated again, now with the formation of the $C_{(6)}$—$C_{(7)}$ double bond [81].



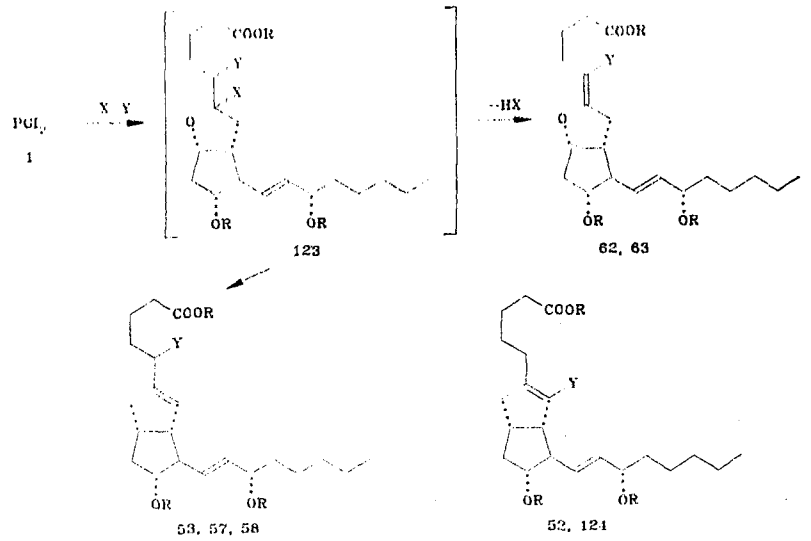
1, 15 21, 45

1 [81], 45 [81, 82] X=O; 15 [111], 21 [57, 58] X=S

This reaction may also take place in the opposite direction (likewise through the addition-elimination of a nucleophile — in this case, water) when a fluorine or a chlorine atom is present in position 5 of the initial Δ^6-isomer; thus, the transformations of (55) and (58) into (61) and (62) have been performed [91, 92].

The reduction of 9(O)-aza-6,9α-dehydro-PGI_1 (23) leads to the two 6-epimers of compound (27) [59]. A widely used method of modifying natural PGI_2 is the addition of aprotic agents to the $C_{(5)}$—$C_{(6)}$ double bond. The adduct so obtained cannot be isolated and decomposed again with the formation of a multiple bond in the $C_{(5,6)}$ or $C_{(6,7)}$ position, but now the prostanoid molecule contains an electrophilic substituent (scheme 15). Together with compounds of types (62), (63), (53), (57), and (58), the isomerization products (52 and (124) are sometimes formed. The use of benzenesulfenyl chloride as modifying agent and the isomerization reaction that has been mentioned permits the formation of 7-hydroxy-substituted prostacyclins (65) [89, 90], and through them also the fluorinated prostacyclin (67) [90]. The chlorination of prostacyclin (58) has led to the dichloro derivative (59) [92].

Scheme 15



1 123 62, 63 53, 57, 58 52, 124

52, 63 Y=SC_6H_5 [88—90]; 53 Y=β-SC_6H_5 [89, 90]; 57 Y=Br [91]; 58 [92], 62 [91], 124 Y=Cl

It was mentioned at the very beginning of this review that in addition to those considered, another whole series of analogues and derivatives of prostacyclin retaining only a rough superficial resemblance to it exists [16, 20]; there is also a group of prostacyclins modified in the periphery of the molecule where the substituent no longer affects the chemical stability of the enol ether grouping of PGI_2. We have been able to discuss the chemical properties of analogues of PGI_1 and also their syntheses only in fragmentary fashion. Nevertheless, in our opinion, the material considered in the present review gives a fairly complete idea of the chemistry of the modified prostacyclins; by the methods that have been considered it is also possible to obtain other, very different, substituted prostanoids, including those with a modifying group in the periphery of the molecule. Already it is clear that the prostacyclins are extremely reactive compounds and their use as the starting materials for obtaining new biologically active compounds of this series with greater efficiency and with a selective action is only in its initial stage. Broad investigations in this respect taking into account the accessibility of the chemical precursor of the prostacyclins ($PGF_{2\alpha}$, which can be obtained

by chemical synthesis) are extremely real and urgent at the present time. The authors hope that this review — the first in the domestic literature on this subject — will serve as a definite stimulus to the development of broader investigations of the prostanoids in our country in the very near future.

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REACTION OF 1-ALKYL-2-ARYL-3-(2-METHYL-2,3-EPOXYPROPIONYL)AZIRIDINES WITH BORON TRIFLUORIDE ETHERATE IN METHANOL

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The reaction of boron trifluoride etherate in methanol with trans-1-methyl(ethyl)- or cis-1-cyclohexyl-2-aryl-3-(2-methyl-2,3-epoxypropionyl)aziridines leads to the formation of the corresponding boron fluoride complexes on the nitrogen atom of the aziridine ring. Reaction with trans-1-cyclohexyl-2-phenyl-3-(2-methyl-2,3-epoxypropionyl)aziridines occurs with stereospecific opening of the aziridine ring to give diastereomeric 2-methyl-5-methoxy-5-phenyl-4-cyclohexylamino-1,2-epoxypentan-3-ones, as well as products from the opening of the epoxide and aziridine rings — tetrahydrofuranones and tetrahydropyranones.

The presence of the epoxide and aziridine rings in the epoxypropionylaziridine molecules makes it possible to compare their reactivity towards a number of reagents. It is known that Lewis acids are widely used as catalysts in reactions of oxiranes and ethyleneimines with nucleophilic reagents [1, 2]. In this connection, the conversions on treatment with boron trifluoride etherate in methanol of the diastereomeric 1-alkyl-2-aryl-3-epoxypropionylaziridines synthesized previously [3] are studied in the present work.

It has been established that the nature of the proeucts formed is dependent on the size of the alkyl substituent at the nitrogen atom of the aziridine ring, while in the case of

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