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^{13}C NMR SPECTROSCOPY OF PROSTAGLANDINS

2. PROSTANOIDS WITH OXYGEN AT C9 AND THEIR INTERMEDIATES*

Introduction

During the past two decades the synthesis of prostaglandins (PGs) has been one of the favourite fields of study of synthetic chemists [3]. Minor changes in PG structure, including configuration changes at one of several asymmetric centers induce drastic alterations in PG activity [4, 5]. It becomes obvious that these specific features require precise and reliable methods for determining the structure and configuration of PGs as well as their intermediates. Up to now, both ^{1}H and ^{13}C NMR spectroscopies have established themselves as reliable and accurate methods in the structure-configuration-conformation studies of PGs and related compounds [6–29].

Despite its several advantages over ^{1}H NMR, ^{13}C NMR has found a more limited use, and only a few specialized ^{13}C NMR studies of PGs and similar compounds have appeared [21–25, 29, 32]. ^{13}C NMR has been mostly used as a complementary method to ^{1}H NMR [6, 8, 10, 11, 16, 27, 30, 31, 33–41] and in many cases ^{13}C chemical shifts are incorrectly assigned [12, 16, 21, 25, 27] or not (completely) assigned [10, 11, 25, 31]. A wide range of PG intermediates has not been characterized by ^{13}C NMR. Therefore we feel that it is about time to fill the gap and present here ^{13}C chemical shifts of a variety of PGs, their intermediates and analogues, as well as correct the mistakes in previous assignments.

Experimental

^{13}C NMR spectra were recorded on WH-90 (22.63 MHz for ^{13}C), CXP-200 (50.31 MHz), CXP-360 (90.55 MHz), and AM-500 (125.76 MHz) «Bruker» spectrometers in $CDCl_3$ solutions at ambient temperature. The deuterated solvent was also used for field-frequency stabilization. ^{13}C chemical shifts were measured in ppm downfield from internal tetramethylsilane (TMS). In most cases signal multiplicities were determined either by off-resonance decoupling or by J-modulated spin-echo [42] using gated decoupling method [43–46]. Many of the compounds (unless indicated otherwise) were synthesized in the Department of Prostanoid Chemistry, Institute of Chemistry (Estonian Academy of Sciences). The synthetic procedures are described elsewhere [39–41].

* Prostaglandin nomenclature will be used throughout this series according to [1, 2]. For previous paper, see [29].

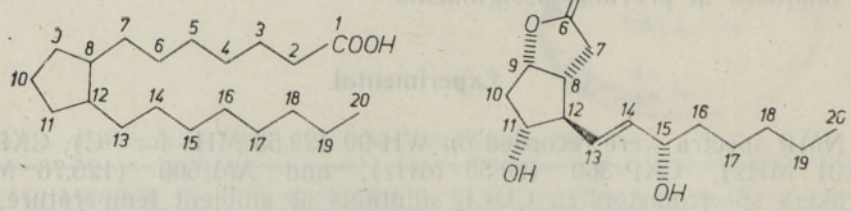
Results and discussion

A. General considerations. The structures and configurations of most of the studied compounds (i. e. the junction of rings and relative orientation of substituents to each other) are known from chemical evidence, chromatographic (TLC) and spectroscopic (UV, IR) data, and agree with both the expected and observed ^{13}C chemical shifts. This allows to focus our attention 1) upon the study of the conformational behaviour of various PGs and their intermediates, and 2) upon the investigation of the conformational dependence of ^{13}C chemical shifts.

In the present report we make use of the exo,endo notation for two purposes: 1) to indicate the diastereoisomerism-related orientation of a substituent relative to the plane of the molecule encompassing carbon nuclei C7 to C10, C12 and oxygen at C9 (see Chart I and Fig. 1 for numbering of carbon atoms; exo corresponds to upwards and endo to downwards orientation of a substituent); 2) to indicate the spatial arrangement of the 5-membered rings in *cis*-bicyclo[3.3.0]octane derivatives related to different conformations of the compounds (see e.g. Fig. 1 and Chart III, V). The exo-conformation here denotes upwards orientation, and endo — downwards orientation of C6 (or, equivalently, C11) relative to the rest of the molecule (see also Fig. 1 and Chart II, V). The cyclopentyl ring (carbon atoms C8 through C12) in bicyclo[3.3.0]octane related compounds is designated as ring *A*, while the lactone ring (or ether ring in some compounds) is designated as *B*. Hence, an exo,endo notation indicates exo-conformation for ring *A* and endo-conformation for ring *B*, etc.

B. PG intermediates. ^{13}C chemical shifts of PG intermediates with oxygen at C9 are summarized in Fig. 1. In addition to regular intermediates, Fig. 1 also contains some irregular and unexpected products for comparison purposes. To facilitate direct comparison with PGs and hence to avoid confusion, the numbering of PG intermediates in Fig. 1 follows the PG numbering [1, 2] rather than the IUPAC rules (see Chart I and compound (1) in Fig. 1).

Chart I



The assignment of ^{13}C resonances of lactone Grieco (1) and the corresponding endo-epoxide (2) is straightforward on the basis of signal multiplicities. The chemical shifts of these compounds agree well with those calculated on the basis of 4-butyrolactone, epoxy-cyclopentane [47], tetrahydrofuran (THF) [48], and bicyclo[3.3.0]octane derivatives [49]. Based on the comparison of calculated shifts for exo-and endo-epoxy lactone Grieco derivatives, lactone epoxide (2) is determined to have endo-configuration. This is also in accordance with chemical evidence. The conformation of the rings is assumed endo,endo for both, (1) and

(2), as revealed by the inspection of Dreiding models and comparison of carbon resonaces in (1) and (2). The endo,endo-conformation of lactone epoxide (2) allows to avoid eclipsing of C7 and epoxide oxygen, which is not possible in exo,endo or exo,exo-conformations. The endo-conformation of ring *B* (lactone ring) is deduced from the conformational analysis of prostacyclins (see section C), and from the inspection of the resonances of respective ^{13}C nuclei in (1) to (16) (discussed below, see also section C).

Lactone derivatives (3) to (5) are assigned according to lactone epoxide (2). The conformation of ring *A* in (3) to (5) is assigned endo as in (2), while that of ring *B* will be discussed in detail later.

The C7 resonances in (3) to (7) are within a few ppm from the calculated shifts. The diamagnetic shift of ca 10 ppm, observed by introduction of carbonyl function into THF [47, 48] is absent here (compare (2) and (3)). Taking also into account bromine's γ-effect, we expect C7 in (3), (4) to be shielded with respect to (6) and (7) by ca 2—3 ppm. However, nearly equal shieldings are observed.

Based on ^1H NMR data and TLC behaviour, the conformations of model compounds (6) and (7) [19] are assigned exo,endo and exo,exo, respectively. It should be noted that ^{13}C chemical shifts of these two diastereoisomers had been mistakenly interchanged in the original paper[19]. Hence, this approximately equal shielding of C7 in (3), (4), (6) and (7) is due to different conformations of ring *A* in (3) and (4) (endo), and in (6) and (7) (exo).

The basis of current conformation assignments will be discussed in greater detail in section C together with respective prostacyclins.

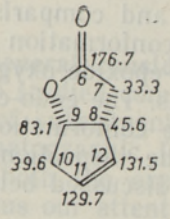
The assigned conformations can also be proved by comparison of the respective ^{13}C chemical shifts of compounds (1) to (4), and (6) to (10).

Furnished by chemical evidence, the acetone-ketal blocked diol (8) has been assigned the *cis,syn,cis*-configuration. C7 shifts in (2) and (8) are within 1 ppm, indicating very similar structures for these compounds. C7 resonances at 33.5 and 30.2 ppm in (9) and (2), respectively, agree well with the calculated less than 3 ppm difference for C7 between exo- and endo-lactone epoxides, confirming the *trans* appendage of —OAc groups at C11 and C12 (this unexpectedly small difference could be attributed to the change in ring *A* conformation). Similarly, the deshielding of C7 by 2.6 ppm is observed in (9) as compared to (8), providing further support to the assumed conformations.

Based both on chemical evidence and examination of molecular models together with carbon chemical shifts results in the *cis,anti,trans*-configuration for the unusual Prins reaction product (10) [82]. Owing to the *trans* junction of the 1,3-dioxane moiety in chair conformation, compound (10) is assigned exo,endo-conformation of rings *A* and *B*, respectively.

It is known that an oxygen atom, even in γ-anti orientation, produces more profound diamagnetic shielding on a γ-carbon than a carbon atom in the same position [48, 50]. Thus, the change in the shielding of C7 in (10) by 3.6 ppm as compared to (2) can be associated with both the substitution of a $—CH_2—$ function in (10) for the epoxide unit in (2), and change of ring *A* conformation from endo (2) to exo (10). Ring *B* maintains endo-conformation in (10) as well as in (2), the reasons for which will be discussed below and in section C.

The acetone-ketal blocked lactone (8) has been assigned *cis,syn,cis*-configuration as depicted in Fig. 1 with exo,endo-conformation of rings *A* and *B*, and exo-conformation of the ketal ring. In such conformation, steric repulsion between C7 and ketal oxygen should be minimal.



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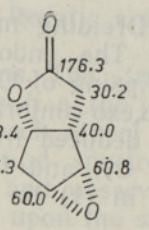

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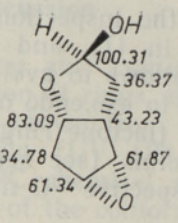

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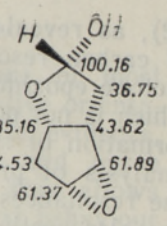

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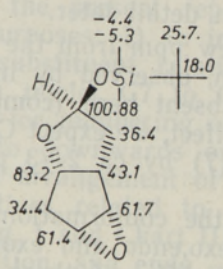

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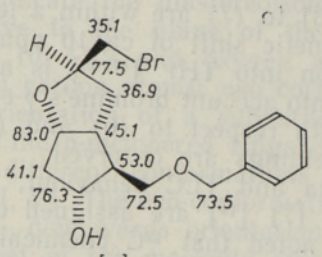

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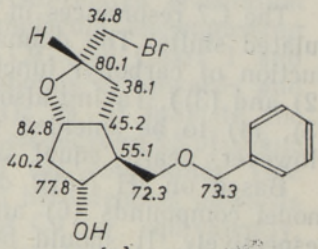

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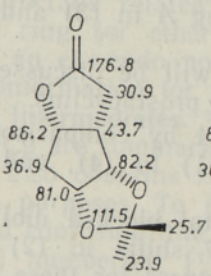

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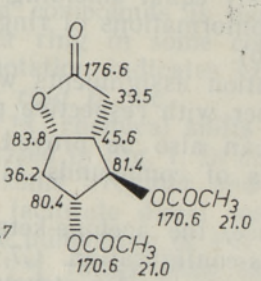

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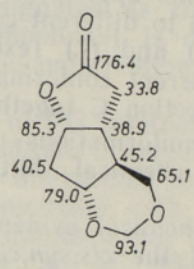

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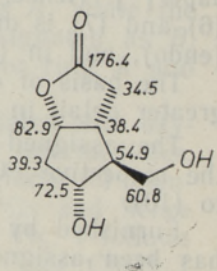

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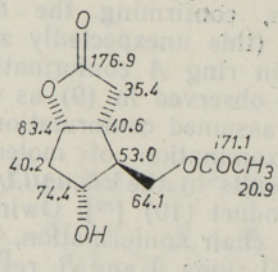

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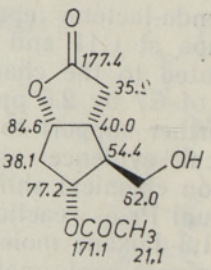

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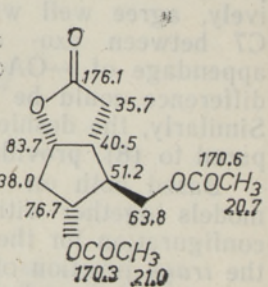

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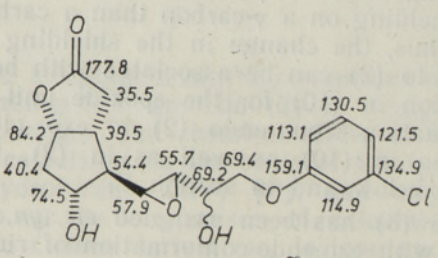
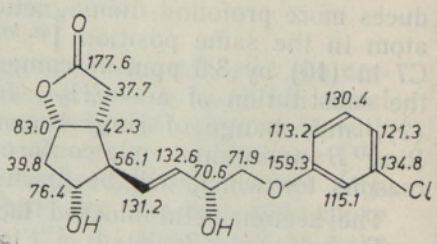


(15)



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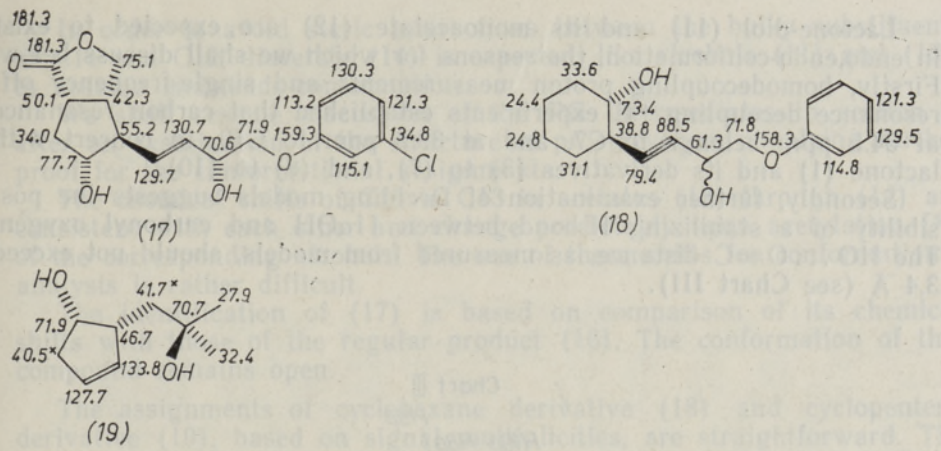


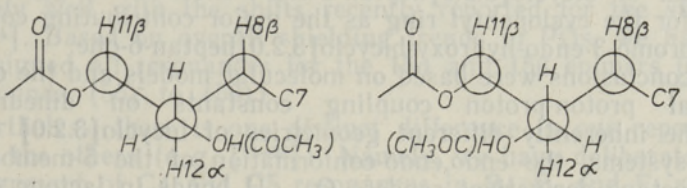
Fig. 1. ^{13}C chemical shifts of some prostaglandin intermediates with C9 oxygen.

Diacetate (9) has been assigned *trans* appendage of the acetyl moieties and endo,endo-conformation of the rings to avoid steric crowding of the bulky substituents at C11 and C12.

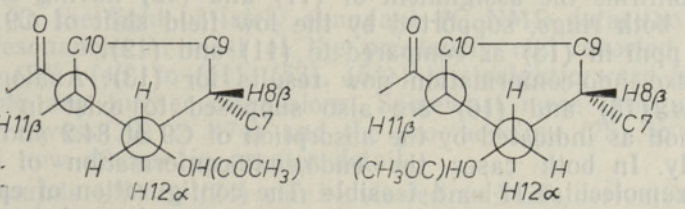
Comparison of the chemical shifts of (8) and (9) clearly indicates that change of ring *A* conformation from exo (8) to endo (9) is again accompanied by shielding of C7 and C9 by 2.6 and 2.4 ppm, respectively. This gives further support to the assignment of the conformations of (3) to (10).

Inspection of the chemical shifts of lactone derivatives (11) to (16) suggests that the key role in determining their conformations belongs to the orientation of C11 and C12 substituents. Examination of Dreiding models and Newman projections of compound (13) (and (14)) along C13—C12 bond (see Chart II) shows us that conformer I should be preferred in exo,endo-conformation of the rings, and conformer IV should be favoured in case of endo,endo-conformation of rings *A* and *B*. Deshielding of C7 and C8, and shielding of C10 and C11 would result in conformer IV relative to conformer I.

Chart II



I exo,endo *II* exo,endo

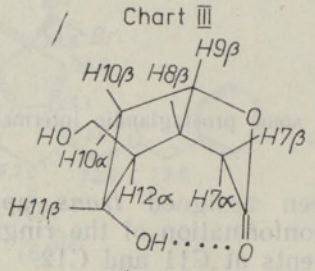


III endo, endo *IV* endo, endo

Lactone-diol (11) and its monoacetate (12) are expected to exist in endo,endo-conformation, the reasons for which we shall discuss below. Firstly, homodecoupling proton measurements and single-frequency off-resonance decoupling ^{13}C experiments established that carbon resonance at 34.5 ppm belongs to C7, and at 39.3 ppm to C10, in concert with lactone (1) and its derivatives (3) to (7), and (8) to (10).

Secondly, further examination of Dreiding models suggests the possibility of a stabilizing H-bond between 11αOH and carbonyl oxygen. The HO . . . O=C distance, as measured from models, should not exceed 3.4 Å (see Chart III).

Chart III



endo, endo

A similar phenomenon has been described by R. F. Newton and co-workers in their study of 2,3-endo-epoxy-bicyclo[3.2.0]heptanone ethylene acetal reactions [51]. For 2-endo-alkyl-3-endo-hydroxy-bicyclo[3.2.0]-heptanone ethylene acetal they suggest a limiting endo-envelope of the 5-membered ring with pseudo-axial orientation of substituents. Their assumption is supported by IR and ^1H NMR data. The O . . . O distance, estimated from a Dreiding model, is ca 2.7 Å [51]. Likewise, for 2-endo-hydroxy-3-exo-alkyl isomer, the endo-envelope conformation, but with pseudo-equatorial substituents, is also favoured. The other alternative for the latter compound is exo-envelope with pseudo-axial substituents and possible hydrogen bonding (O . . . O distance ca 3.4 Å), outruled, however, by IR data [51].

Z. Grudzinsky and S. M. Roberts [52] have investigated electrophilic bromination of bicyclo[3.2.0]heptan-2-ene-6-ones and suggest an endo-envelope for the cyclopentyl ring as the major contributing conformation in 2-exo-bromo-3-endo-hydroxy-bicyclo[3.2.0]heptan-6-one.

Their conclusions were based on molecular models and the dependence of vicinal proton-proton coupling constants on dihedral angle. Despite the inherently different geometries of bicyclo[3.2.0] and bicyclo[3.3.0] systems, the endo,endo-conformation of the 5-membered rings in bicyclooctane derivatives renders O . . . H bonds in lactone derivatives (11) and (12) still possible.

This confirms the assignment of (11) and (12) having endo-conformation of both rings, supported by the low field shift of C9 resonance by ca 1.2 ppm in (13) as compared to (11) and (12).

Also, exo,endo-conformation now results for (13). Analogously, the compounds (15) and (16) are also supposed to exist in endo,endo-conformation as indicated by the absorption of C9 at 84.2 and 83.0 ppm, respectively. In both cases the endo,endo-conformation of the rings makes intramolecular H-bond feasible. The configuration of epoxide unit in (15) is assumed *trans*, otherwise severe repulsion between vicinal groups would result.

In order to avoid steric interactions between the bulky substituents at C11 and C12, diacetate (14) is expected, like alcohols (11) and (12), to assume endo,endo-conformation.

We shall resume discussion of the PG intermediates in section C after an examination of the structure of prostacyclins, supplying further proof for the conformational assignments.

The chemical shifts of C10 to C13 in acetates (12) through (14) are consistent with each other and change predictably upon acetylation [53] of the corresponding alcohols. The use of these shifts for conformational analysis is rather difficult.

The identification of (17) is based on comparison of its chemical shifts with those of the regular product (16). The conformation of this compound remains open.

The assignments of cyclohexane derivative (18) and cyclopentene derivative (19), based on signal multiplicities, are straightforward. The relative orientations of hydroxyl and alkyl groups in (18) and (19) are known from chemical evidence and are confirmed by ^{13}C chemical shifts.

C. Prostaglandins with oxygen at C9 and their analogues. ^{13}C chemical shifts of prostanoids with oxygen at C9 are summarized in Fig. 2. Along with PGs synthesized in the Institute of Chemistry (Estonian Academy of Sciences) (compounds (20), (22) to (24), (29) to (55), (72) to (74), (79) and (80)) (cf. [29, 39–41]), ^{13}C chemical shifts for many other PGs, encountered in the literature, are presented as well. We hope this would provide a base for further assignment of PG ^{13}C NMR spectra and serve as a valuable analytical tool.

The basic principles and assignment of resonances in ^{13}C NMR spectra to individual carbons in the PG skeleton have been discussed at length in earlier studies, and for full details an interested reader is referred to the original papers of G. Lukács et al. [21], G. F. Cooper and J. Fried [22], G. Kovács et al. [25], B. D. Polis et al. [28], and T. Pehk et al. [29]. Several misassignments made in earlier papers are corrected in our previous report on this subject [29]. It must be noted, however, that the chemical shifts of C15 and C16 in 16-phenoxy-derivatives of 11-deoxy-PGE_1 in [29] should be interchanged.

But for a few exceptions, the results obtained in our laboratory agree well with literature data, even without taking into account the experimental differences (e. g. temperature, concentration, etc.).

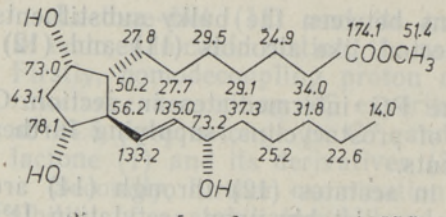
The chemical shifts of 11-deoxy-PGE_1 derivatives (36) to (51) agree reasonably well with the shifts recently reported for the similar PGE_2 series [54]. Based on overall shielding trends in PGs, we have conclusively assigned all resonances for the 15α and 15β epimers in [54] (Fig. 2, compounds (56) to (59)).

Nevertheless, there is one distinct difference in our reports as compared to the others (e. g. [21–28]). Namely, we have deliberately reversed the assignment of C4 and C5 resonances in B_1, E_1 and F_1 series, based on quantitative considerations of ^{13}C chemical shifts of PGs and model alkanes [55].

Thus, in the light of fairly abundant ^{13}C NMR data, the assignment of ^{13}C resonances in most of the previously not reported prostanoids ((29) to (34), (46) to (51), (53), (54)) is straightforward and does not necessitate any further discussions. Somewhat more intriguing are the PG derivatives (72) to (74) and the prostacyclins (75) to (92), which we shall now discuss in greater detail.

Compounds (72) to (74) can be viewed as PGF_2 derivatives, allowing an insight into the steric interactions involved in $PGF_{2\alpha}$ and $PGF_{2\beta}$.

The early work on ^{13}C relaxation times and vicinal proton-proton



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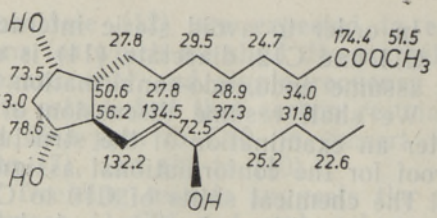

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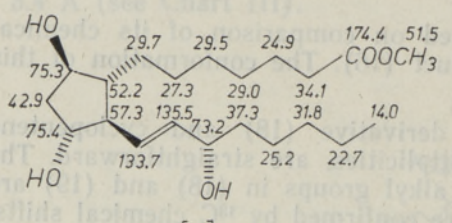

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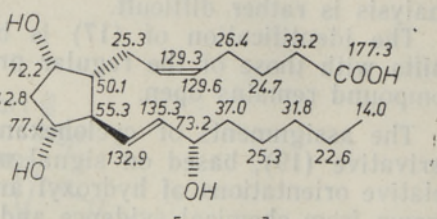
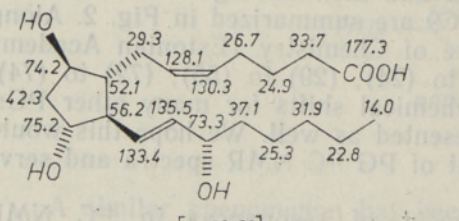
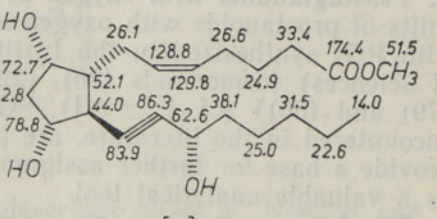


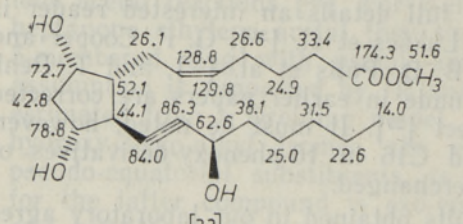
(23) [21-23,29]



(24) [21,22,29]



(25) [22]



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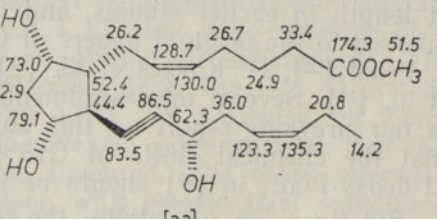

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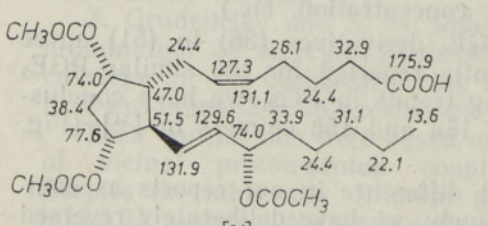

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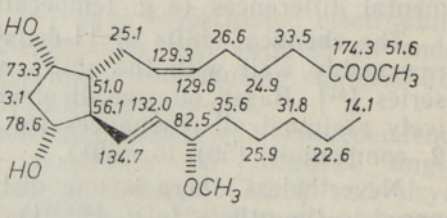

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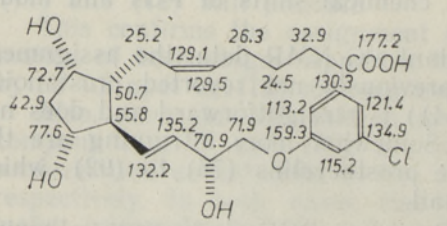

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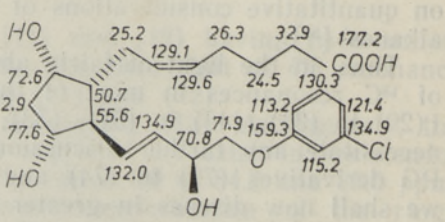

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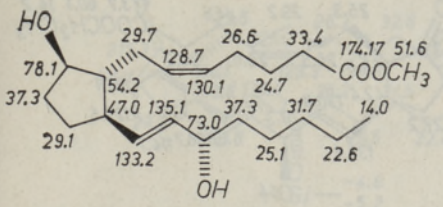

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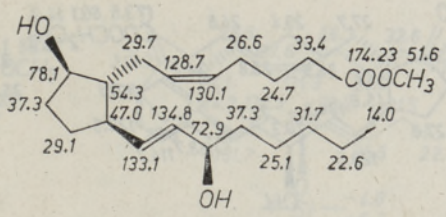

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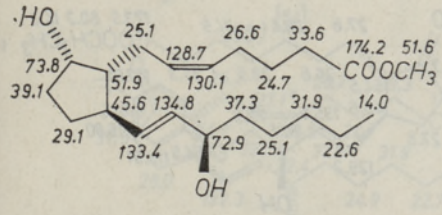

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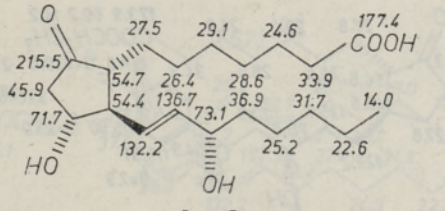

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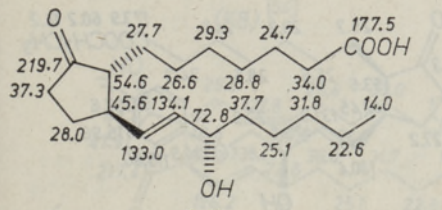

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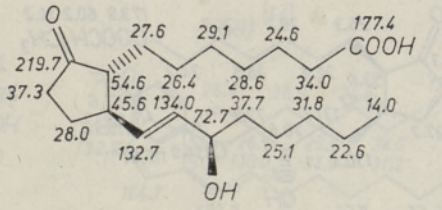

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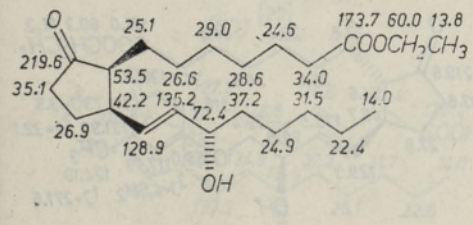

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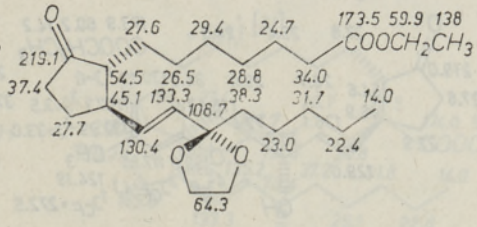

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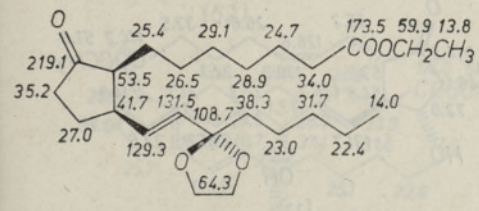

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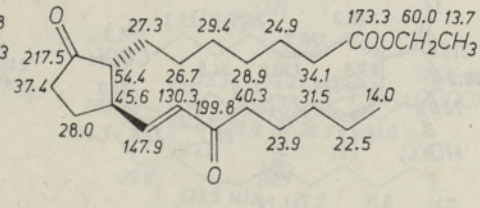

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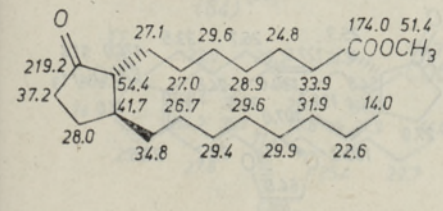

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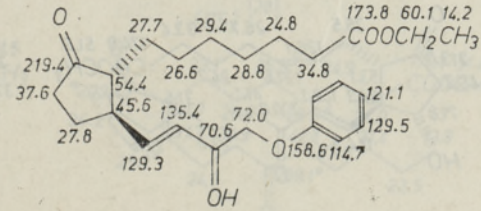

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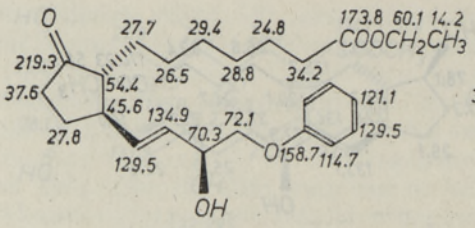

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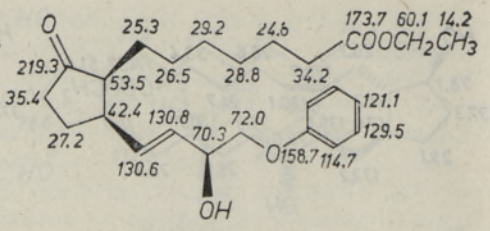

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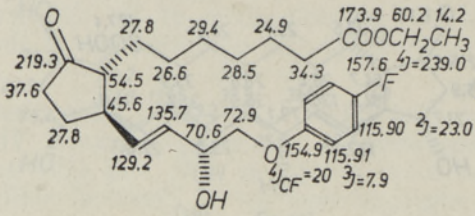

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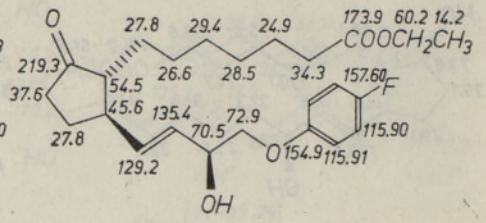

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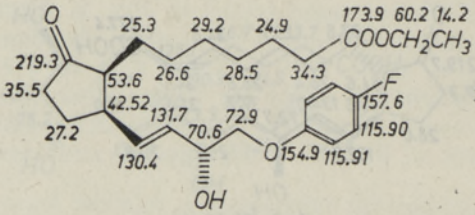

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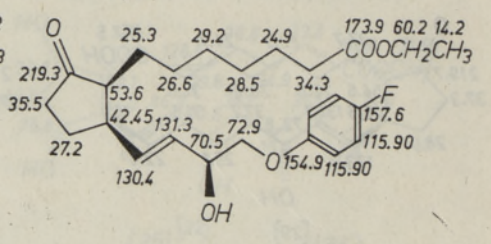

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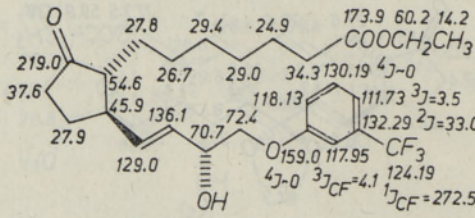

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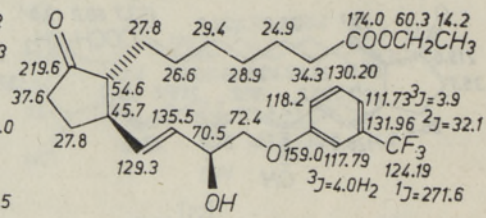

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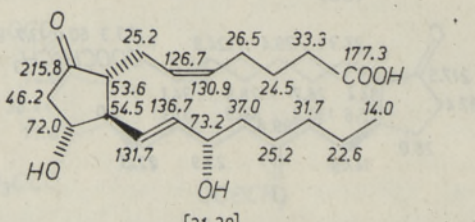

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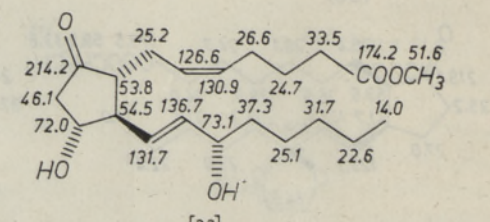

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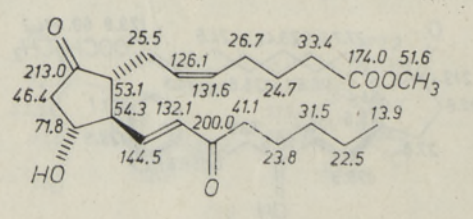

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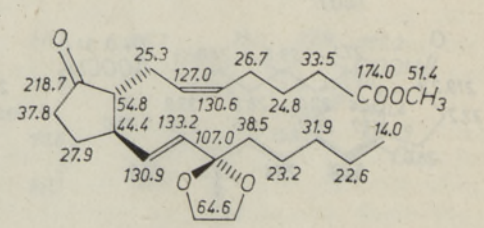

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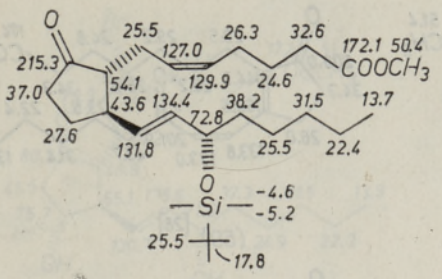

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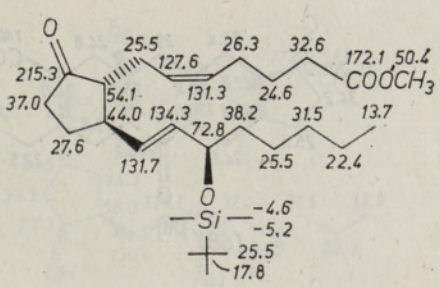

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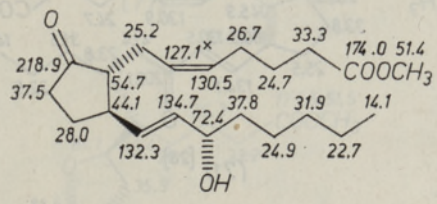

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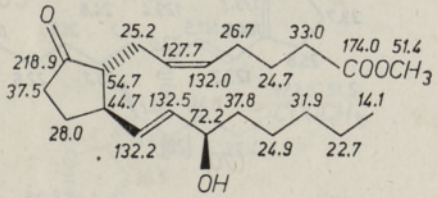

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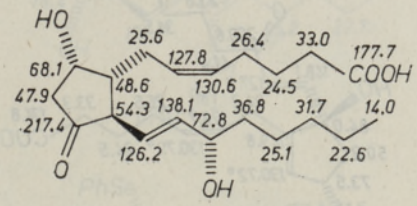

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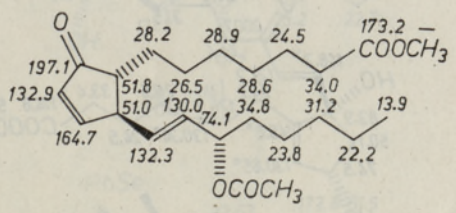

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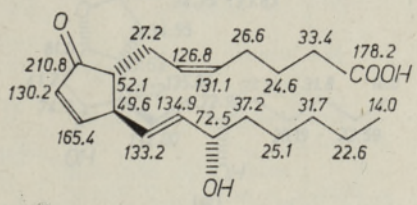

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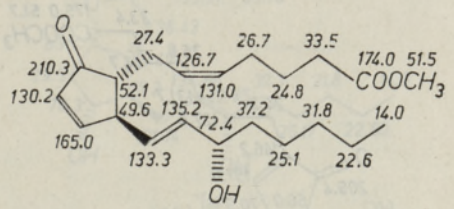

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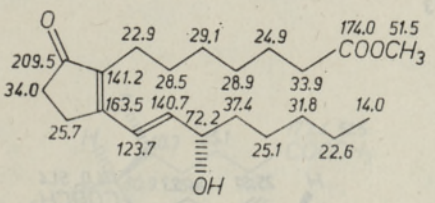

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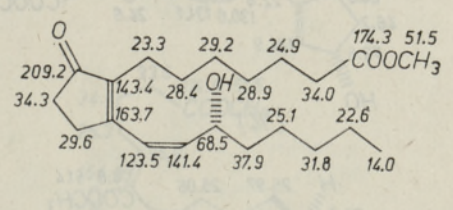

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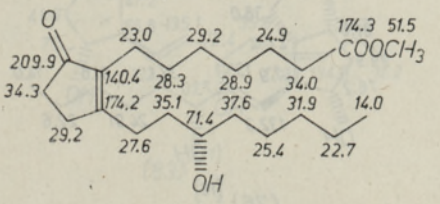

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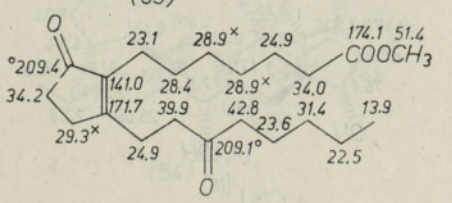

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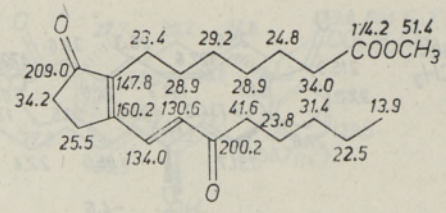

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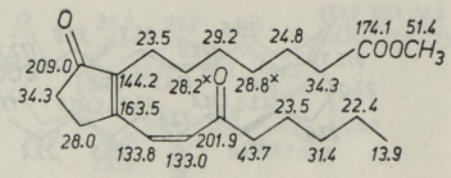

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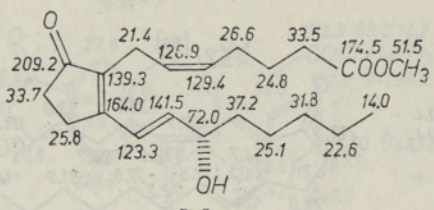

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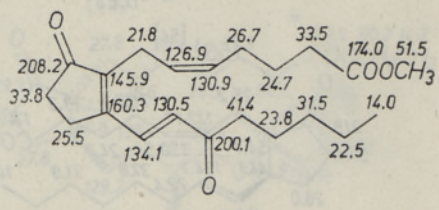

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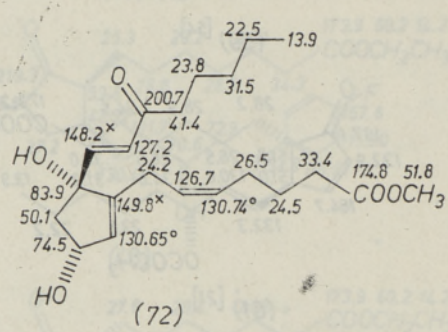

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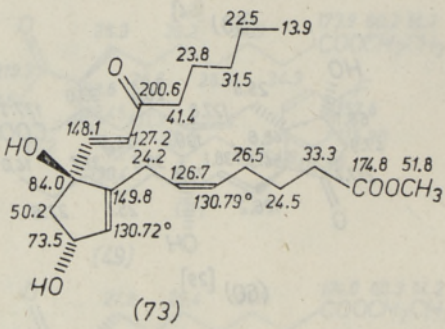

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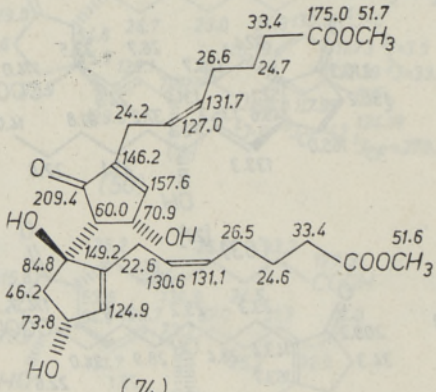

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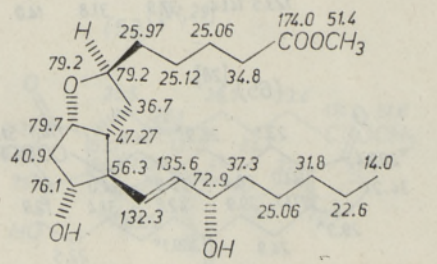

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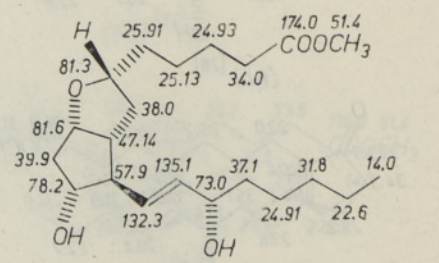

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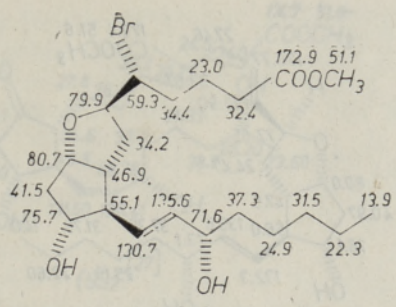

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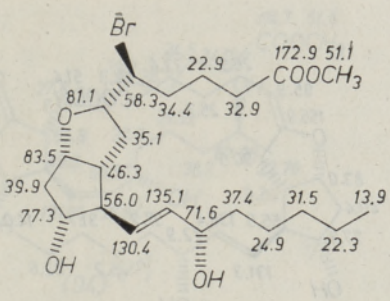

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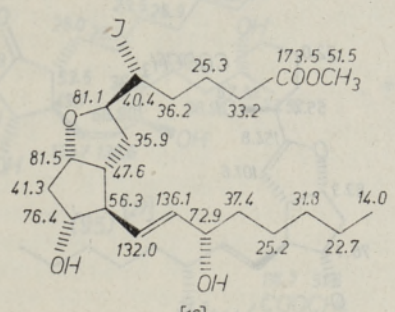

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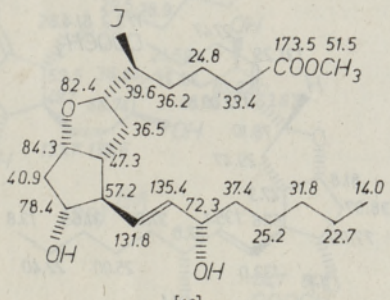

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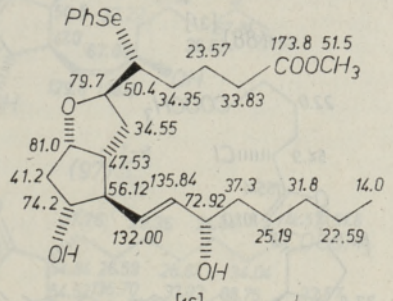

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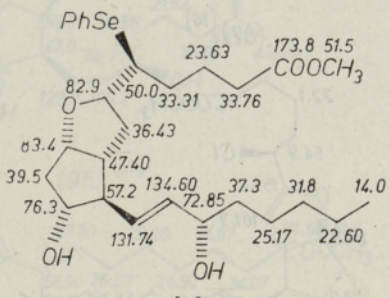

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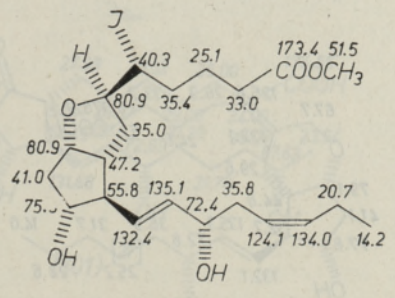
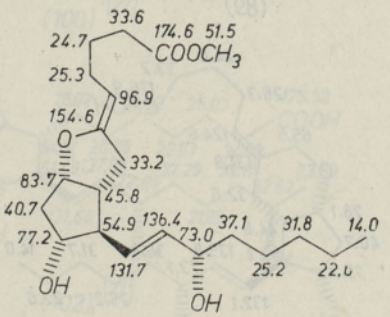
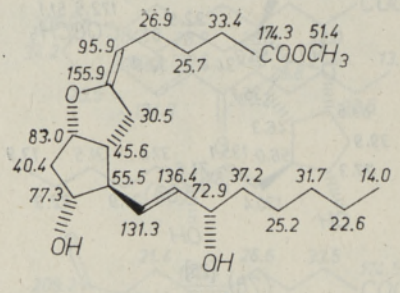


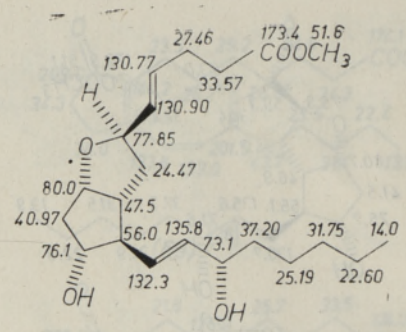
(83) [11]



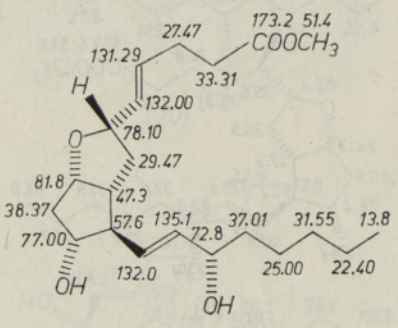
(84) [8,11]



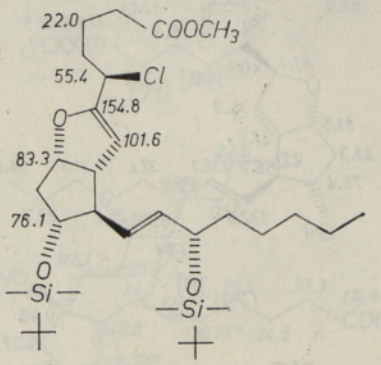
(85) [8, 11]



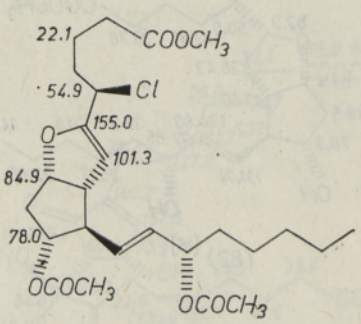
(86) [16]



(87) [16]



(88) [31]



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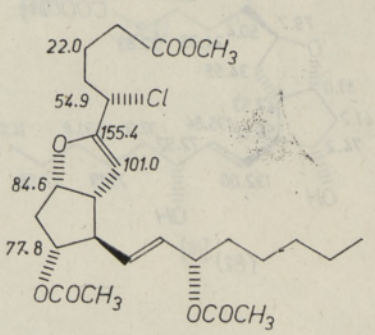
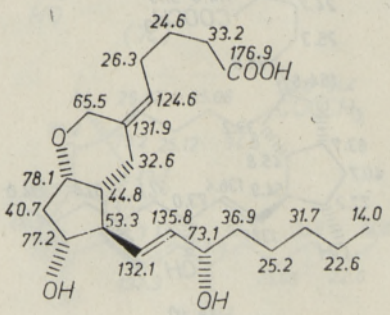
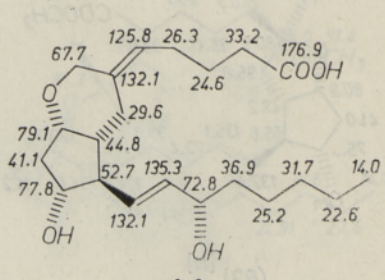


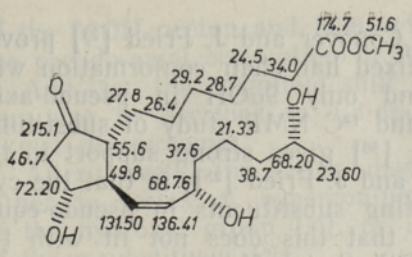
(90) [31]



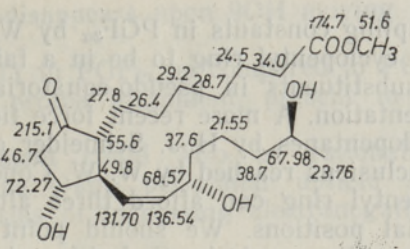
(91) [18]



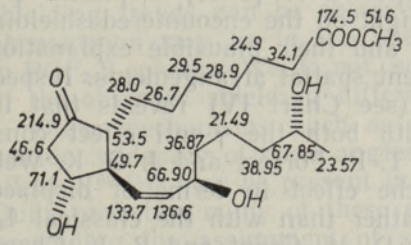
(92) [18]



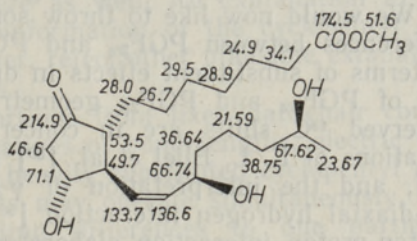
(93) [27]



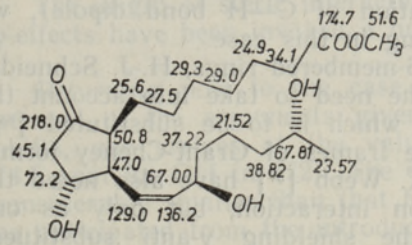
(94) [27]



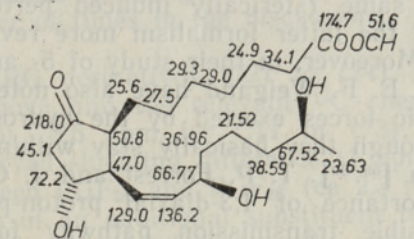
(95) [27]



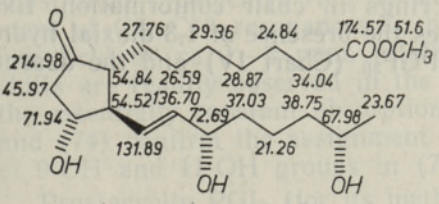
(96) [27]



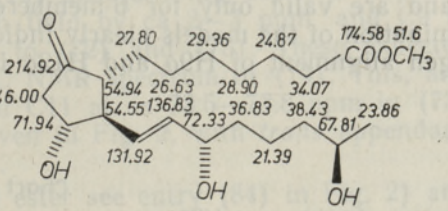
(97) [27]



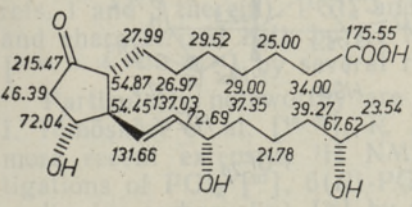
(98) [27]



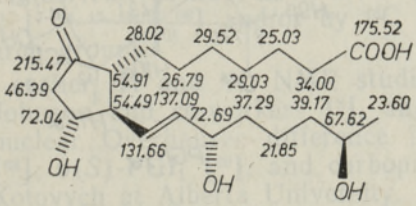
(99) [27]



(100) [27]



(101) [27]



(102) [27]

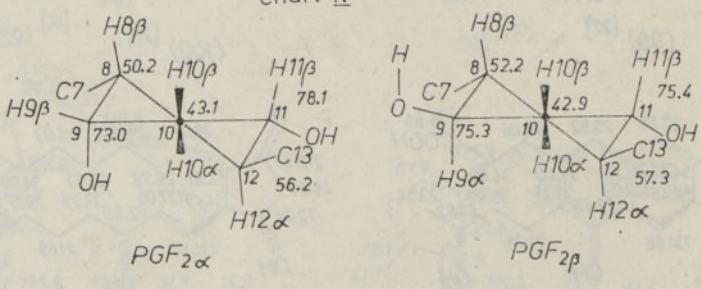
Fig. 2. ^{13}C chemical shifts of prostanoids with C9 oxygen.
X, O — chemical shifts of those carbons may be interchanged within a compound.

coupling constants in $PGF_{2\alpha}$ by W. W. Conover and J. Fried [23] proved the cyclopentyl ring to be in a fairly fixed half-chair conformation with 3 substituents in pseudo-equatorial and only 9αOH in pseudo-axial orientation. A more recent force field and ^{13}C NMR study of substituted cyclopentanes by H.-J. Schneider et al. [56] gives strong support to the conclusions reached by W. W. Conover and J. Fried [23], in that the cyclopentyl ring can afford three alternating substituents in pseudo-equatorial positions. We should point out that this does not fit with the assumption made by G. Lukács et al. [21], that a H-bond exists between 9αOH and C5=C6 bond. The assignment of $PGF_{2\alpha}$ and $PGF_{2\beta}$ has been confirmed by investigating ^{13}C spectra of [9-^{2}H] 9-epimers [22].

We would now like to throw some light on the encountered shielding differences between $PGF_{2\alpha}$ and $PGF_{2\beta}$ and their plausible explanations in terms of substituent effects in different spatial arrangements. Inspection of $PGF_{2\alpha}$ and $PGF_{2\beta}$ geometries (see Chart IV) reveals that the observed ^{13}C shifts are in concert with both the γ-anti effect considerations of E. L. Eliel et al. [50] and T. P. Forrest and J. G. K. Webb [57], and the interpretation of γ-gauche effect in terms of displaced 1,3-diaxial hydrogen interaction [58], rather than with the classical 1,4-proton-proton interaction elaborated by D. M. Grant and B. V. Cheney [59–63]. Although it can be argued that the rationale behind the different approaches of D. M. Grant [59–63] and H. Beierbeck [58] is essentially the same (sterically induced perturbation of C—H bond dipole), we find the latter formalism more revealing in this case.

Moreover, in their study of 5- and 6-membered rings, H.-J. Schneider and E. F. Weigand have also noted the need to take into account the steric forces exerted by the hydrogen which is to be substituted [64], although they basically stay within the frames of Grant-Cheney formalism [59–63]. T. P. Forrest and J. G. K. Webb [57] have also noted the importance of 1,3-diaxial proton-proton interaction, but only as one possible transmission pathway for the shielding γ-anti substituent effects of the first-row elements. On the other hand, H. Beierbeck [58] has emphasized that their substituent effects have been derived from and are valid only for 6-membered rings in chair conformation. Examination of the models clearly indicates the presence of 1,3-diaxial hydrogen alignment of H9α and H12α in $PGF_{2\beta}$ (Chart IV) and the absence

Chart IV



of such an arrangement in $PGF_{2\alpha}$, which, in Beierbeck's formalism, presumably accounts for the observed displacements of C9 and C12 resonances to low field in $PGF_{2\beta}$ as compared to $PGF_{2\alpha}$ by ca 2.0 and 1.1 ppm, respectively. In the same manner, the downfield shift of C8 resonance by ca 2.0 ppm can be associated with 1,3-diaxial alignment

of the 9βOH proton and H8β, which disappears upon 9OH moving into the pseudo-axial orientation in $PGF_{2\alpha}$.

And last, the downfield shift of C11 in $PGF_{2\alpha}$ as compared to $PGF_{2\beta}$ can also be ascribed to 1,3-diaxial proton alignment, present in the former diastereomer.

Alternatively, the latter displacement could also be rationalized either in terms of hyperconjugatative γ-anti periplanar upfield shift of the hydroxyl group [50], or in terms of increasing electronegativity of the γ-substituent [57].

We are aware, of course, that the 1,3-diaxial alignment is not as explicit in cyclopentane as it is in cyclohexane, but the same general shielding trends can be observed here as well. An explanation to this phenomenon may lie in the fixed conformation of the cyclopentyl ring in PGF_2 9-epimers. We do not, however, reject other plausible exlanations of the observed shielding differences.

Other mechanisms, such as distortions from fixed half-chair conformation, widening of bond angles, changes of bond lengths, electric field effects [64, 65], may be present in the heavily substituted cyclopentyl ring. Quite probably, many of these effects may operate simultaneously, thus precluding the assignment of shielding differences to one particular mechanism. Clearly, a comprehensive quantum chemical treatment, providing fully relaxed molecular geometries, would be necessary.

The origin of steric interaction effects is ambiguous as yet, although γ-effects have been invoked a number of times in the discussions.

Returning now to the case of PG derivatives (72) to (74), after perusal of the arguments given above and the relevant ^{13}C chemical shifts, one arrives at the value of 73.5 ppm for C11 in (73), and 74.5 ppm for C11 in (72). The observed shielding difference (1 ppm) is considerably smaller than that between $PGF_{2\alpha}$ and $PGF_{2\beta}$ (ca 2.3 ppm), as anticipated from the introduction of an additional substituent to C9. Assignment of the remaining resonances is trivial, the only ambiguity is associated with the sp^2 carbons C5 and C6. The attachment of a substituted cyclopentyl ring to C9 (74) should bring about a displacement of C7, C10 resonances to high field by ca 2—3 ppm, and C9 to low field by ca 1—2 ppm, relative to (72) and (73). These expected shifts are readily observed in the ^{13}C NMR spectrum of (74). This, and the essentially constant absorption of C11 at ca 73.5—73.8 ppm in (73) and (74) confirm the assignment given in Fig. 2, with *trans* appendage of 9-OH and 11-OH groups in (74).

Prostacyclin PGI_2 (for its methyl ester see entry (84) in Fig. 2) and its analogues (75) to (92) have aroused great interest as highly potent platelet aggregation inhibitors (cf. [8] and refs. 1—5 therein; [66] and refs. 1 and 3 therein). PGI_x and their derivatives have been investigated and characterized both by ^1H NMR [7–11, 15, 18, 31, 66] and/or by ^{13}C NMR [8, 10, 11, 15, 18, 25, 26, 31] by several research groups.

Particularly noteworthy are the earlier ^1H and ^{13}C NMR studies of I. Tömösközi et al. [10, 35], R. A. Johnson and co-workers [8], and the more recent extensive ^1H NMR nuclear Overhauser difference investigations of PGI_2 [67], 6(*R*)-PGI_1 [68], 6(*S*)-PGI_1 [69], and carboprostacyclin (or carbacyclin) [70] by G. Kotovych at Alberta University.

Now, in order to assert the assignment of the ^{13}C resonances of prostacyclins, we should first analyse and compare their conformations, which has not, to our knowledge, been done yet. To illuminate the relative orientation of the substituents and the conformations of the 5-membered rings in prostacyclins, we have estimated the proton-proton dihedral angles φ, utilizing a Karplus-type equation [71–73] (see the Table):

Geminal and vicinal HH′ coupling constants (Hz) and estimated dihedral angles * (deg) in some prostaglandins and prostacyclins

HH′	g/c/t	PGE_2 [78]		$PGF_{2\alpha}$ [25]		PGI_2 [67]		6*R*-PGI_1 [68]		6*S*-PGI_1 [69]		carba-PGI_2 [70]	
		J	φ	J	φ	J	φ	J	φ	J	φ	J	φ
6α5	t	—	—	—	—	—	—	—	—	6.3	135	—	—
6β5	t	—	—	—	—	—	—	6.3	135	—	—	—	—
6α7α	c	5.8	40	—	—	—	—	—	—	4.6	50	—	—
6α7β	t	5.8	135	—	—	—	—	—	—	10.4	160	—	—
6β7α	t	5.8	135	—	—	—	—	9.1	150	—	—	—	—
6β7β	c	5.8	40	—	—	—	—	6.3	40	—	—	—	—
6aα6aβ	g	—	—	—	—	—	—	—	—	—	—	15.0	—
6aα9β	t	—	—	—	—	—	—	—	—	—	—	2.0	110
6aβ9β	c	—	—	—	—	—	—	—	—	—	—	8.9	20
7α7β	g	14.8	—	—	—	15.5	—	12.0	—	12.4	—	14.8	—
7α8β	t	5.8	135	—	—	0	90	5.0	130	0.5	95	0.5	95
7β8β	c	5.8	40	—	—	7.6	30	9.1	20	8.1	25	8.7	20
8β9β	c	—	—	—	—	6.5	35	7.2	30	7.6	30	8.7	20
8β12α	t	11.6	180	11.4	180	10.7	165	9.7	155	10.0	160	9.7	155
9β10α	t	—	—	6.0	140	3.0	120	4.4	125	6.0	135	7.7	145
9β10β	c	—	—	—	—	7.2	30	7.2	30	7.6	30	8.2	25
10α10β	g	18.4	—	14.4	—	14.3	—	13.6	—	12.9	—	12.2	—
10α11β	t	9.8	155	8.4	150	8.7	150	9.3	155	10.5	160	10.0	160
10β11β	c	7.4	30	—	—	8.7	20	7.2	30	6.8	35	7.0	35
11β12α	t	8.6	150	7.2	140	8.7	150	9.3	155	10.0	160	9.8	155
12α13	t	8.3	145	8.4	150	—	—	—	—	—	—	8.1	145
14,15β	t	6.6	140	—	—	6.5	135	—	—	6.6	140	6.7	140
15,16	t	6.6	140	—	—	6.5	135	6.7	140	6.6	140	6.7	140

* Estimated, using ${}^3J^0{}_{max}=10.0$ Hz, ${}^3J^{180}{}_{max}=11.5$ Hz, last digit rounded to nearest 0 or 5 deg.

$$^3J_{HH'}=A\cos^2\varphi+B\cos\varphi+C.$$

Although the results of such calculations should be treated with precaution [72], we think the approach is justified as long as molecules with similar structural features are compared. Also, it would be most instructive to gain at least qualitative assessments of the different conformations in various prostacyclins. Calculations of dihedral angles according to more recently proposed relationships [74–77] did not yield better results.

In addition, one should always bear in mind the fact that the observed coupling constants will be time-averaged mean values if more than one conformation contributes to the J value (e. g. pseudorotation of the cyclopentyl ring), and so the dihedral angles will represent a mean conformation.

The solution conformation of $PGF_{2\alpha}$ was ascertained by W. W. Conover and J. Fried from $^3J_{HH'}$ and X-ray data, and was discussed above, while that of PGE_2 was determined by G. Kotovych and G. H. M. Aarts [78]. Their results are given in the Table for comparison. Inspection of the respective coupling constants and dihedral angles reveals that both prostaglandins exist in a fixed half-chair conformation, as was also proposed in [6].

Examination of molecular geometries and molecular models suggests that prostacyclins assume twisted envelope conformation of both 5-membered rings designated as *A* and *B* (see Chart V), the flat part of the molecules encompassing C8 and C9. The conformation of ring *A* (i. e.

carbon atoms C8 to C12) can be assessed via *trans* vicinal coupling constant between protons H8β and H12α ($J_{8\beta12\alpha}$), H9β and H10α ($J_{9\beta10\alpha}$), H10α and H11β ($J_{10\alpha11\beta}$), H11β and H12α ($J_{11\beta12\alpha}$), and *cis* vicinal coupling constants between protons H8β and H9β ($J_{8\beta9\beta}$), H9β and H10β ($J_{9\beta10\beta}$), H10β and H11β ($J_{10\beta11\beta}$), and the corresponding dihedral angles.

Estimated dihedral angles (the Table) and molecular models indicate that all prostacyclins assume twisted exo-envelope-conformation for ring *A*. The observed coupling constants as well as conformations deduced from them represent mean values. However, the values of $J_{8\beta12\alpha}$ corresponding to nearly 180° dihedral angles suggest that exo-conformation of ring *A* is the major contributing conformation in our cases.

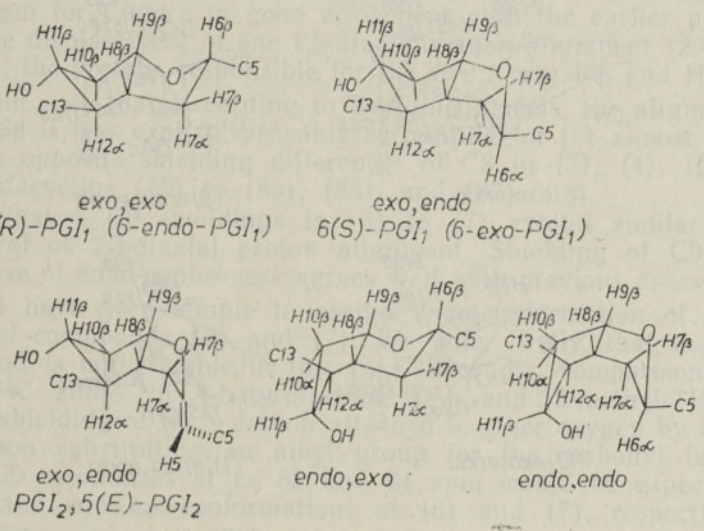
The slightly elevated values of $^3J_{HH'}$ involving H9 in carbacyclin are exceptions, and reflect mainly the substitution of 6a carbon in carbacyclin for the more electronegative C9 oxygen in PGI_2 [70].

Comparison of the results obtained by G. Kotovych for 6(*R*)-PGI_1 in D_2O and $CDCl_3$ (not presented in the Table) [68] suggests nearly identical conformation for 6(*R*)-PGI_1 in these 2 different solvents, although both rings, *A* and *B*, appear to be somewhat flattened in $CDCl_3$ solution.

We thus note that according to $^3J_{HH'}$ and the estimated dihedral angles, ring *A* adopts twisted exo-envelope in prostacyclins contrary to some bicyclic PG intermediates discussed in section B.

Now, as to the conformation of ring *B* (carbon atoms C6 to C9), the relevant coupling constants to be considered are $J_{7\alpha8\beta}$, $J_{7\beta8\beta}$, and also $J_{6a\alpha9\beta}$ and $J_{6a\beta9\beta}$ for carbacyclin. The data in the Table clearly indicate the dependence of ring *B* conformation upon the nature and orientation of the substituent at C6. Hence, on the basis of the estimated dihedral angles $\varphi_{7\alpha8\beta}$ and $\varphi_{7\beta8\beta}$, one arrives at the endo-envelope for ring *B* in PGI_2 (PGI_2 methyl ester — (84)), 6(*S*)-PGI_1 (or 6-exo-PGI_1, entry (75) in Fig. 2, methyl ester) and carbacyclin; and exo-envelope for ring B in 6(*R*)-PGI_1 (or 6-endo-PGI_1, entry (76) in Fig. 2, methyl ester). The respective conformations are also depicted in Chart V.

Chart V



Observations of nuclear Overhauser enhancement from H5 to H7α in PGI_2 [67] and in carbacyclin [70] not only indicate *Z*-configurations

of the C5=C6 double bonds [67, 70], but also verify the close spatial proximity of the protons under question in PGI_2 and carbacyclin, thus confirming the assumption of an endo-envelope for ring B in these compounds. It has been stated, however, that pseudorotation occurs more readily in PGI_2 than in carbacyclin [70]; thus, ring *B* is essentially flattened in PGI_2 and carbacyclin as well. This should also apply to ring *B* in PGI_1s and to ring *A* in all compounds, although to a lesser extent, as can be assessed from $^3J_{HH'}$ and $\varphi_{HH'}$ values. On the other hand, substituents at C11 and C12 force ring *A* into a more or less fixed exo-envelope conformation with a maximum number of substituents in pseudo-equatorial orientation.

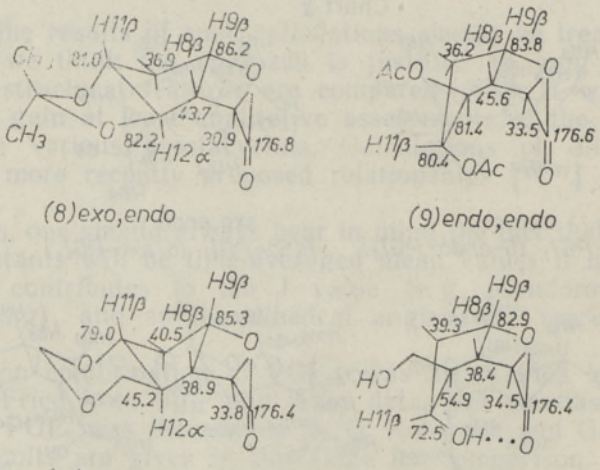
The influence of 6-substituents in PGI_1 series depends on their orientation and can be summarized as follows: 6-exo-substituent (e. g. 6(*S*)-PGI_1 (75), 5(*R*)-halogeno-6(*R*)-PGI_1 (77), (79)) forces ring *B* into endo-envelope. A 6-endo-substituent, on the contrary, forces ring *B* into exo-envelope (e. g. 6(*R*)-PGI_1 (76), 5(*S*)-halogeno-6(*S*)-PGI_1 (78), (80)). In both cases substituents at C6 retain pseudo-equatorial orientations to avoid unfavourable 1,3-syn-diaxial interactions with C10 and C12. The above arguments apply to all prostacyclins with asymmetric centers at C6, except 9-deoxy-6,9a-methano-epoxy-5(*E*)/5(*Z*)-PGE_{1S} (91) and (92) [18], which should be considered separately.

In the light of the conformational arguments, a reconsideration of PG intermediates would be quite instructive. The scheme forwarded by H. Beierbeck [58], and proved by us to work in 5-membered rings as well, will be used again.

Let us first refocus our attention upon the conformations of ring *A* and carbon-13 chemical shifts in compounds (3) to (16).

Again, the structures of (8) through (11) should be compared for these purposes. The conformations of the above compounds (discussed also in section B) as well as their most relevant chemical shifts are depicted in Chart VI.

Chart VI



Comparison of C9 resonances in these substances reveals that the change of ring *A* conformation from exo to endo is accompanied by shielding of the particular resonance by 2.4 ppm in both pairs ((8) and (9), (10) and (11)). Such a shielding effect can, according to H. Beierbeck

[58], be attributed to the disappearance of 1,3-diaxial alignment of H9β and H11β in the endo-conformation of ring *A* ((9), (11)). Likewise, shielding of C10, C11 and C12 in (9) with respect to (8), and of C8 in (11) with respect to (10), although to a lesser extent, could be explained in terms of removed 1,3-diaxial proton-proton alignment. The observed smaller than expected changes may be assigned to steric crowding, i. e. to a nearly eclipsed orientation of C7 and the substituent at C12 in the exo,endo-conformers (8) and (10), which is relieved in endo,endo-conformation of the 5-membered rings of (9) and (11). Such a relief of steric repulsion should also account for the unexpected deshielding of C8 in (9), as compared to its counterpart in the exo,endo-conformer (8). As discussed in section B, eclipsing of C7 and C12 substituent could be avoided in the endo,endo-conformation of lactone epoxide (2). This was assumed to be responsible for the relatively small shielding of C7 in endo,endo-conformation of (2) as compared to the exo,endo-conformation of (8).

We can now ascribe the shielding of C9 by 2.4 ppm to the change in the conformation of one ring from exo to endo, or, to be more precise, to the displacement of one 1,3-diaxial proton-proton alignment. C9 resonance at 82.0 to 83.8 ppm can hence be assigned to lactone derivatives in endo,endo-conformation. Analogously, C9 absorption at 85.3 to 86.2 ppm can be assigned to similar derivatives in exo,endo-conformation.

Thus, inspection of the data in Fig. 1 clearly indicates that compounds (9), (11), (12) and (14) to (16) exist in endo,endo-conformation, while compounds (8), (10) and (13) exist in exo,endo-conformation, confirming the assumptions made in section B. The endo,endo-conformations are additionally stabilized by an intramolecular H-bond (see Section B and Chart III), or are caused by a relief of spatial crowding (compound (14)).

The conformation of ring *B* (lactone or ether ring), as ascertained from the conformational analysis of prostacyclins, is endo for 6-exo substituted compounds (3), (5) and (6), and exo for 6-endo diastereoisomers, such as (4) and (7). The observed chemical shift differences of ca 2.6 ppm for C6 are in good agreement with the earlier proposed value for the displacement of one 1,3-diaxial proton alignment (2.4 ppm). In this case, the protons responsible for the effect are H6β and H9β.

We should note that, according to Dreiding models, the alignment of H6β and H8β is less explicit, probably accounting for the almost vanishing or even opposite shielding differences of C8 in (3), (4), (6), (7), and in prostacyclins (75) to (83), (86), and (87).

As anticipated, C9 shieldings in (3) to (7) exhibit similar trends upon removal of 1,3-diaxial proton alignment. Shielding of C9 by ca 2 ppm in case of endo-conformers agrees well with previous assessments.

It would have been simple to assign endo-conformation of ring *A* to the model compounds (6) and (7). We note, firstly, that the stabilizing H-bond is not possible in this case. Secondly, comparison of the respective ^{13}C shifts in 4-butyrolactone [47] and 2-methyl-THF [48] indicates a shielding of the γ-carbon attached to ether oxygen by at least 1.1 ppm upon substituting an alkyl group for the carbonyl function. Therefore, C9 resonances at ca 82 and 84 ppm would be expected for endo,endo- and endo,exo-conformations of (6) and (7), respectively.

Instead, absorptions at 83.0 and 84.8 ppm are detected, suggesting an exo-conformation for ring *A*, both in (6) and (7). Further support is provided by the observed shieldings of C7 and C12 in (6) as compared to (7) by 1.2 and 2.1 ppm, respectively, arising from the removal of H7α-H12α alignment in (6) (see Chart VI). Shielding of C11 in (6)

with respect to (7) is, in concert with prostacyclins (75) to (82), ascribed to steric compression of C11 and the endo-oriented ring *B* in the former compound. No 1,3-diaxial proton interaction responsible for such a shielding could be found.

Hence, exo,endo- and exo,exo-conformations are assigned to 6-exo-bromomethyl derivative (6) and 6-endo-bromomethyl derivative (7), respectively.

Interestingly, C6 resonances in the alcohols (3) and (4) are unexpectedly insensitive towards the conformation change of ring B from endo in (3) to exo in (4). The small shielding difference of C7 in (3), as compared to (4), is obviously caused by the proximity of C7 to the oxirane ring in both compounds, rather than by the removal of H12α in (3) and (4) as compared to (6) or (7).

The endo-conformation of ring B is determined from $^3J_{HH'}$ for PGI_2 and carba-I_2 possessing a double bond at C6. Based on analogy, the lactone derivatives (1), (2) and (8) to (16) are also assigned endo-conformation of ring *B* (cf. section *B*).

Obviously, further research is needed to confirm these conformations of PG intermediates, and ^{1}H NMR in high magnetic fields would certainly prove most useful for these purposes.

We can now resume the discussion of prostacyclins and their ^{13}C chemical shifts. The ^{13}C NMR spectra of PGI_2 methyl ester (84) and its 5(E)-diastereoisomer (85) were assigned by R. A. Johnson et al. [8, 11]. The 5(*Z*) and 5(*E*) configurations of the double bond were later confirmed by G. Kotovych et al. [67] by proton NOE difference experiments.

It must be pointed out that ^{13}C NMR provides a clear advantage over ^{1}H NMR here. The assignment of the configuration to 5(*Z*) or 5(*E*) on the basis of the chemical shift difference of C7 resonance by ca 2.7 ppm (33.2 ppm for *trans*- and 30.5 ppm or *cis*-isomer, respectively) is straightforward. Hence, the assignment of 5(*Z*)/5(*E*) isomers is trivial by ^{13}C NMR, being easily performed even in their mixture. The resolution obtainable nowadays permits the resolution of most of the closely lying resonances from the 20 carbons in 5(*Z*)/5(*E*)-diastereoisomers. On the other hand, assignment by ^{1}H NMR requires extensive study of overlapping complex multiplets and employment of various techniques, such as NOE difference measurements, homodecoupling [67], etc. The complexity of proton spectra significantly increases when two or more diastereoisomers are present in the solution.

The assignment of ^{13}C spectra of 6(*S*)-PGI_1 (75) and 6(*R*)-PGI_1 (76), performed by K. C. Nicolaou et al. [16], was based on the previously reported model compounds (6) and (7) [10], 5-bromo-PGI_1s (77), (78) [24, 25], and 5(*R*),6(*R*)-iodo-PGI_1s (79), (80) [8, 11].

Appendage of a halogen atom to C5 changes the absolute configuration at C6 from 6(*S*) to 6(*R*) (i. e. for exo-substituted compounds) and vice versa (for endo-substituted compounds).

The 5(*R*)-configuration has been assigned to 6-exo, i. e. 6(*R*)-derivatives (76), (79), and 5(*S*)-configuration to 6-endo-derivatives (78) and (80), in concert with chemical evidence and mechanistic considerations [11]. The cases of 5-seleno-PGI_1s (81) and (83) [16] are not clear. It is assumed that the configurations at C5 coincide with those of other similar prostacyclins. Furthermore, ^{13}C chemical shifts of 6-exo- and 6-endo-bromoethers (77) and (78) were mistakenly interchanged in the original paper [25]. The correct assignments are given in Fig. 2. Our data on 5-iodo-PGI_1 methyl esters agree with literature data on similar compounds [16, 21].

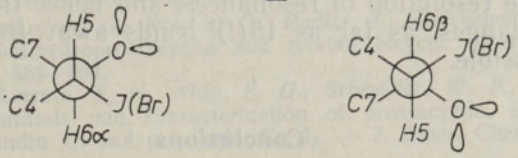
The ^{13}C chemical shift differences of C5 and C6 in diastereoisomeric 5-halogeno-PGI_1s, as calculated from PGI_1s [16] using the latest iodine

and bromine parameters [79, 80], do not agree with experimental data for (77) to (80), except for C5, for which the difference (exp.—calc.) is within 1 ppm. Comparison of the chemical shifts of ethane, haloethanes and 2-haloethanols [81] results in discrepancies between the measured and calculated shifts of ca 6.5 ppm (to lower field with respect to experiment) for C6 in both diastereoisomeric 5-halogeno-PGI_1s (77) to (80).

Similarly, C7s are calculated to resonate at a higher field from the experimental values by ca 2 ppm. The observed shifts are, however, in good agreement with bromine and iodine relative γ-effects in secondary halides [79, 80].

Examination of Newman projections along C5—C6 bond (see Chart VII) reveals that in both diastereoisomers, (79) and (80) (or (77) and (78)), the preferred conformer has the iodine (bromine) atom γ-gauche to C9 oxygen. One plausible explanation of the observed dicrepancies between the experimental and calculated shifts therefore lies in an orbital interaction between oxygen lone pair electrons and iodine (bromine) free orbitals.

Chart VII



5(R)6(R)-halogeno-PGI_1 (exo,endo-conformation)

5(S)6(S)-halogeno-PGI_1 (exo,exo-conformation)

The shielding differences of C6 and C9 between diastereoisomeric PGI_1s and the corresponding halides by 1.2 to 2.1 ppm (cf. Fig. 2) agree well with the established conformations of these compounds (see also the Table and Chart V), and the expected shielding changes upon the change of ring B conformation from exo to endo as discussed above.

The resonances of other nuclei, such as C7, C10, C11 and C12, also follow the expected trends encountered in PG intermediates.

It should be noted, however, that in contrast to the intermediates (3) and (6), C8 nuclei in 6-exo-substituted prostacyclins (75), (77), (79), and (81) are deshielded.

Compared to other prostacyclins the screening differences of C6 (by 3.2 ppm) and C7 (by 1.8 ppm) in diastereoisomeric selenoderivatives (81) and (82) are somewhat enhanced. We have tentatively assigned this to the bulkiness of the PhSe substituent.

Shieldings of the remaining carbon nuclei in 6-exo-PGI_1s (75), (77), (79), (81), (83), 6-endo-PGI_1s (76), (78), (80), (82), 6-exo-4(*E*)-PGI_2 (86), and 6-endo-4(*E*)-PGI_2 (87) agree with those in prostaglandins.

Unfortunately we must point out several misinterpretations made in the assignment of PGI_1s. Firstly, to be consistent with model compounds and other prostacyclins, the assignment of C6 and C9 resonances in 6-exo- and 6-endo-5-iodo-PGI_1s in [16] should be interchanged. For the same reasons we have assigned the resonance at 24.5 ppm to C7 in 6-exo-(*E*)-PGI_2 (86), and that at 29.5 ppm to C7 in 6-endo-4 (*E*)-PGI_2 (87), while C3 absorption should remain uneffected by configurational change **at** C6 as indicated by the nearly constant shift of 27.5 ppm, assigned to that carbon in (86) and (87).

The diamagnetic shift of C7 resonances in 6-exo- and 6-endo-4(*E*)-

PGI_2s (86) and (87) by ca 10 ppm with respect to 6-exo- and 6-endo-PGI_1s (75) and (76), as well as the large shielding difference of C7 by 5 ppm between diastereoisomeric (86) and (87) remain unexplained.

Likewise, the chemical shifts of C3 and C19 in 5-seleno-PGI_1s should be interchanged. The absorptions for C18 at 24.5 ppm, 27.5 ppm, 26.0 ppm, and 25.9 ppm in 6-exo-PGI_1 (75), 6-endo-PGI_1 (76), 6-exo-4(*E*)-PGI_2 (86), and 6-endo-4(*E*)-PGI_2 (87) [16], respectively, and those at 23.6 ppm for C19 in selenoderivatives (86) and (87) are incorrectly assigned to these carbons in [16]. The correct assignments of the above-mentioned compounds are given in Fig. 2. Tentative assignments of 5-chloro-PGI_2s (88) and (89) [10] are also presented there.

R. F. Newton et al. have recently reported ^{13}C chemical shifts of 9-deoxy-6,9a-methanoepoxy-5(*Z*)-prostaglandin F_1 (91), a stable analogue of PGI_2 together with its 5(*E*)-isomer (92) [18]. The shielding differences between these two isomers follow, as anticipated, the general trends found in prostacyclin I_2.

To illustrate the power of ^{13}C NMR again, in Fig. 2 we also present the chemical shifts of 19-hydroxy-PGE_1s ((93) to (102)) [27] (with a few corrections, see [29], and complete assignment of diastereoisomers (93) to (98)), where resolution of resonances, and hence the detection of configurational changes, as far as 15(!) bonds away from the asymmetric center was possible.

Conclusions

The conformations of various prostacyclins have been first ascertained from literature ^1H NMR data, and these conformational arguments were further used to establish relationship between ^{13}C chemical shifts and conformations of prostacyclins using the concepts forwarded by H. Beierbeck et al. [58].

Shielding of C6 and C9 by ca 2—3 ppm was found to be associated with the removal of 1,3-diaxial proton-proton alignment in bicyclic PG intermediates and prostacyclins. Although considerably smaller than the 5 ppm reported by H. Beierbeck et al. [58] in cyclohexyl derivatives, it nevertheless allows one to estimate the conformations of various prostaglandins by natural abundance ^{13}C NMR spectroscopy, and thus provides clearer understanding of ^{13}C shieldings in these compounds.

^{13}C chemical shifts for 102 PGs and their intermediates are given in Figs 1 and 2, hopefully supplying an analytical tool for further studies in the PG field. Research is in progress to clear the few ambiguities still left.

We should like, once more, to point out the inherent power of natural abundance ^{13}C NMR spectroscopy as a structural probe of PGs. On the basis of abundant data, the determination of the structure, configuration and conformation of PGs and their intermediates is mostly straightforward. Resonances of most of the 20 carbon nuclei in the mixtures of diastereoisomers can be resolved and assigned, and shielding differences of carbon nuclei as far as 15 or more bonds from the asymmetric center can be detected and interpreted in PGs and their intermediates [27, 29]. This makes ^{13}C NMR spectroscopy a unique tool for the analysis of PGs, their intermediates and analogues.

The original intention was not writing a review but rather an account on our current research. We are fully aware that not all available data as of writing are included and apologize if some important results have escaped our attention.

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REFERENCES

1. *Nelson, N. A.* Prostaglandin nomenclature. — J. Med. Chem., 1974, **17**, 911—918.
2. *Johnson, R. A., Morton, D. R., Nelson, N. A.* Nomenclature for analogs of prostacyclin (PGI_2) — Prostaglandins, 1978, 15, N 5, 737—751.
3. *Bindra, J. S., Bindra, R.* Prostaglandin Synthesis. New York, 1977.
4. *Floche, L., Bölke, H., Frankus, E., Kim, S.-M. A., Lintz, W., Löschen, G., Michel, G., Müller, B., Schneider, J., Seipp, U., Vollenberg, U., Wilsman, K.* Designing prostacyclin analogues. — Arzneim.-Forsch./Drug Res., 1983, **33**, N 9, 1240—1248
5. *O-Yang, C., Kertesz, D. J., Kluge, A. F., Kuenzler, P., Li, T., Marx, M. M., Bruno, J. J., Chang, L.* Synthesis and platelet aggregation inhibition activity of a series of enantiomeric bicyclo[3.2.0]heptane-6-oximinoacetic acids.—Prostaglandins, 1984, **27**, N 6, 851—863.
6. *Ахрем А. А., Королева Е. В.* Спектроскопия ЯМР в химии простагландинов. — Изв. АН БССР, Сер. хим. наук, 1978, № 6, 103—118.
7. *Fried, J., Barton, J.* Synthesis of 13,14-dehydroprostacyclin methyl ester: a potent inhibitor of platelet aggregation. — Proc. Natl. Acad. Sci. USA, 1977, **74**, 2199—2203.
8. *Johnson, R. A., Lincoln, F. H., Thompson, J. L., Nidy, E. G., Mizsak, S. A., Axen, U.* Synthesis and stereochemistry of prostacyclin and synthesis of 6-ketoprostaglandin $F_{1\alpha}$. — J. Amer. Chem. Soc., 1977, **99**, N 12, 4182—4184.
9. *Nelson, N. A.* Stereoconfiguration of 5,6-dihydroprostacyclins. — J. Amer. Chem. Soc., 1977, **99**, N 22, 7362—7363.
10. *Tömösközi, I., Galambos, G., Kovács, G., Radics, L.* Stereochemistry of 5-bromo- and 5-iodo-5,6-dihydroprostacyclin and related bicyclic ethers. — Tetrahedron Lett., 1978, **6**, 581—584.
11. *Johnson, R. A., Lincoln, F. H., Nidy, E. G., Schneider, W. P., Thompson, J. L., Axen, U.* Synthesis and characterization of prostacyclin, 6-ketoprostaglandin $F_{1\alpha}$, prostaglandin I_1, and prostaglandin I_3. — J. Amer. Chem. Soc., 1978, **100**, N 24, 7690—7705.
12. *Kotovych, G., Aarts, G. H. M.* A high field proton magnetic resonance study of the solution conformation of thromboxane B_2. — Can. J. Chem., 1980, **58**, N 11, 1111—1117.
13. *Nicolaou, K. C., Magolda, R. L., Sipio, W. J., Barnette, W. E., Lysenko, Z., Joullie, M. M.* Phenylselenoetherification. A highly efficient cyclization process for the synthesis of O-and S-heterocycles. — J. Amer. Chem. Soc., 1980, **102**, N 11, 3784—3793.
14. *Paquette, L. A., Crouse, G. D., Sharma, A. K.* A stereocontrolled synthetic entry to the primary prostaglandins from butadiene. Oxy anionic substituent effects on [1,5]-hydrogen sigmatropy. — J. Amer. Chem. Soc., 1980, **102**, N 11, 3972—3974.
15. *Nicolaou, K. C., Barnette, W. E., Magolda, R. L.* Synthesis of (5Z)- and (5E)-6,9-thiaprostacyclins. — J. Amer. Chem. Soc., 1981, **103**, N 12, 3472—3480.
16. *Nicolaou, K. C., Barnette, W. E., Magolda, R. L.* Organoselenium-based synthesis of oxygen-containing prostacyclins. — J. Amer. Chem. Soc., 1981, **103**, N 12, 3480—3485.
17. *Nicolaou, K. C., Barnette, W. E., Magolda, R. L.* Organoselenium-based synthesis of sulfur containing prostacyclins. — J. Amer. Chem. Soc., 1981, **103**, N 12, 3486—3497.
18. *Newton, R. F., Wadsworth, A. H.* Synthesis of stable prostacyclin analogues from 2,3-disubstituted bicyclo[3.2.0]heptan-6-ones. — J. Chem. Soc. Perkin I, 1982, N 3, 823—830.
19. *Lin, C.-H., Alexander, D. L., Chidester, C. G., Gorman, R. R., Johnson, R. A.* 10-Nor-9,11-secoprostaglandins. Synthesis, structure, and endoperoxide analogues. — J. Amer. Chem. Soc., 1982, **104**, N 6, 1621—1628.
20. *Bartmann, W., Beck, G., Knolle, J., Rupp, R. H.* Synthesis of stable prostacyclin analogues. — Tetrahedron Lett., 1982, **23**, N 36, 3647—3650.
21. *Lukacs, G., Piriou, F., Gero, S. D., Dorp, van D. A., Hagaman, E. W., Wenkert, E.* Carbon-13 nuclear magnetic resonance spectroscopy of naturally occurring substances. Prostaglandins. — Tetrahedron. Lett., 1973, **7**, 515—518.
22. *Cooper, G. F., Fried, J.* Carbon-13 nuclear magnetic resonance spectra of prostaglandins and some prostaglandin analogs. — Proc. Natl. Acad. Sci. USA, 1973, **70**, N 5, 1579—1584.
23. *Conover, W. W., Fried, J.* Carbon-13 relaxation and proton nuclear magnetic resonance studies of prostaglandin $F_{2\alpha}$. — Proc. Natl. Acad. Sci. USA, 1974, **71**, N 6, 2157—2161.
24. *Rackham, D. M., Cowdrey, S. E., Gutteridge, N. A., Osborne, D. J.* N.m.r. spectra of prostaglandin metabolites and precursors and of related pyrazoline adducts. — Org. Magn. Reson., 1977, **9**, N 3, 160—163.

25. *Tömösközi, I., Galambos, G., Simonidesz, V., Kovács, G.* A simple synthesis of PGI_2. — Tetrahedron Lett., 1977, **30**, 2627—2628.
26. *Corey, E. J., Pearce, H. L., Szekely, I., Ishiguro, M.* Configuration at C-6 of 6,9a-oxido-bridged prostaglandins. — Tetrahedron Lett., 1978, **12**, 1023—1026.
27. *Lüthy, C., Konstantin, P., Untch, K. G.* Total synthesis of dl-19-hydroxyprostaglandin E_1 and dl-13-*cis*-15-epi-19-hydroxyprostaglandin E_1. — J. Amer. Chem. Soc., 1978, **100**, N 19, 6211—6217.
28. *Polis, B. D., Polis, E., Kwong, S.* ^{13}C nuclear magnetic resonance studies of prostaglandin B monomers as an approach to elucidation of the structure of PGB_X, a prostaglandin B polymer. — Physiol. Chem. and Physics, 1981, **13**, 111—119.
29. *Пехк Т., Вялимяэ Т., Самель Н., Лопп М., Лилле Ю., Липпмаа Э.* Спектроскопия ^{13}C-ЯМР простагландинов. — Изв. АН ЭССР. Хим., 1982, **31**, № 2, 85—90.
30. *Coughlin, D. J., Brown, R. S., Salomon, R. G.* The prostaglandin endoperoxide nucleus and related bicyclic peroxides. Synthetic and spectroscopic studies. — J. Amer. Chem. Soc., 1979, **101**, N 6, 1533—1539.
31. *Bannai, K., Toru, T., Oba, T., Tanaka, T., Okamura, N., Watanabe, K., Hazato, A., Kurozumi, S.* Halogenation of PGI_2-enol ether with N-halosuccinimide: synthesis of new stable PGI_2 analogs, 5-chloro- and 5,7-dichloro-PGI_2. — Tetrahedron Lett., 1982, **23**, N 36, 3707—3710.
32. *Crombie, L., Pattender, G., Simmonds, D. J.* Carbon-13 nuclear magnetic resonance spectra of the natural pyrethrins and related compounds. — J. Chem. Soc. Perkin I, 1975, N 15, 1500—1502.
33. *Morton, D. R., Brokaw, F. C.* Total synthesis of 6a-carbaprostaglandin I_2 and related isomers — J. Org. Chem., 1979, **44**, N 16, 2880—2887.
34. *Scarborough, R. M., Toder, B. H., Smith III, A. B.* A stereospecific total synthesis (±)-methylenomycin A and its epimer, (±)-epimethylenomycin A. — J. Amer. Chem. Soc., 1980, **102**, N 11, 3904—3913.
35. *O'Connor, D. E., Michelich, E. D., Coleman, M. C.* Isolation and characterization of bicyclo endoperoxides derived from methyl linolenate. — J. Amer. Chem. Soc., 1981, **103**, N 1, 223—224.
36. *Riedike, M., Schwarz, J.* Mercury(II)-induced cyclization of acetylenic alcohols: a new route to enol ethers and substituted enol ethers. — J. Amer. Chem. Soc., 1982, **104**, N 21, 5842—5844.
37. *O'Connor, D. E., Michelich, E. D., Coleman, M. C.* Stereochemical course of the autooxidative cyclization of lipid hydroxyperoxides to prostaglandin-like bicyclo endoperoxides. — J. Amer. Chem. Soc., 1984, **106**, N 12, 3577—3584.
38. *Bhagwat, S. S., Hamann, P. R., Still, W. C.* Synthesis of thromboxane A_2. — J. Amer. Chem. Soc., 1985, **107**, N 22, 6372—6376.
39. *Lopp, M., Parve, O., Lõhmus, M., Pals, A., Välimäe, T., Lille, Ü.* Synthesis of prostanoids via alkynyl borate oxirane ring opening. — Proc. ESOC IV, Aix-en-Provence, Sept. 2—6, 1985.
40. *Парве О., Пальс А., Лыхмус М., Вялимяэ Т., Лопп М., Лилле Ю.* Синтез простагландинов F и I ряда. 1. Синтез (±)простагландина $F_{2\alpha}$ и (±)(9)-дезокси-Δ^5-6,9α-циклопростагландина F_1. — Изв. АН ЭССР. Хим., 1985, **34**, № 4, 276—284.
41. *Парве О., Пальс А., Лыхмус М., Вялимяэ Т., Лахе Л., Лопп М., Лилле Ю.* Синтез простагландинов F и I ряда. 2. Синтез (±)13,14-дидегидро-6,9α-метано-простагландина I_2 через этиленовый кеталь 2,3-эндо-эпоксибицикло[3.3.0]-октан-7-она. — Изв. АН ЭССР. Хим., 1985, **34**, № 4, 285—291.
42. *Rabenstein, D. R., Nakashima, T. T.* Spin-echo Fourier transform nuclear magnetic resonance spectroscopy. — Anal. Chem., 1979, **51**, N 14, 1465A—1474A.
43. *Cookson, D. J., Smith, B. E.* Improved methods for assignment of multiplicity in ^{13}C NMR spectroscopy with applications to the analysis of mixtures. — Org. Magn. Reson., 1981, **16**, N 2, 111—117.
44. *LeCocq, C., Lallemand, J.-Y.* Precise carbon-13 N. M. R. multiplicity determination. — J. Chem. Soc. Chem. Commun., 1981, **4**, 150—152.
45. *Patt, S. L., Shoolery, J. N.* Attached proton test for Carbon-13 NMR. — J. Magn. Reson., 1982, **46**, N 3, 535—539.
46. *Elgert, K.-F., Kosfeld, R., Hull, W. E.* Selective assignments in ^{13}C NMR spectra of chloroalkanes by J-modulated ^{13}C spin echo. — J. Magn. Reson., 1984, **56**, N 1, 1—9.
47. *Bremser, W., Ernst, L., Franke, B., Gerhards, R., Hardt, A.* Carbon-13 NMR Spectral Data. Weinheim, 1981.
48. *Eliel, E. L., Pietrusiewicz, K. M.* Topics in Carbon-13 NMR Spectroscopy. New York, 1979, **3**, 177—211.
49. *Whitesell, J. K., Matthews, R. S.* Carbon-13 chemical shifts in bicyclo[3.3.0]octanes. — J. Org. Chem., 1977, **42**, N 24, 3878—3882.
50. *Eliel, E. L., Bailey, W. F., Kopp, L. D., Willer, R. L., Grant, D. M., Bertrand, R., Christensen, K. A., Dalling, D. K., Duch, M. W., Wenkert, E., Schell, F. M.,*

Cochran, D. W. Carbon-13 magnetic resonance. Upfield shifts caused by nitrogen, oxygen, and fluorine atoms located at the gamma position and antiperiplanar to the nucleus observed. — J. Amer. Chem. Soc., 1975, **97**, N 2, 322—330.

51. *Cave, R. J., Howard, C. C., Klinkert, G., Newton, R. F., Reynolds, D. P., Wadsworth, A. H., Roberts, S. M.* Regioselective reactions of 2,3-endo-epoxybicyclo[3.2.0]heptanone ethylene acetal involving organometallic reagents. — J. Chem. Soc. Perkin I, 1979, N 12, 2954—2958.
52. *Grudzinsky, Z., Roberts, S. M.* Electrophilic bromination of bicyclo[3.2.0]hept-2-en-6-ones. — J. Chem. Soc. Perkin I, 1975, N 18, 1767—1773.
53. *Christl, M., Reich, H. J., Roberts, J. D.* Nuclear magnetic resonance spectroscopy. Carbon-13 chemical shifts of methylcyclohexanes, cyclopentanols and cyclopentyl acetates. — J. Amer. Chem. Soc., 1971, **93**, N 34, 3463—3468.
54. *Luo, F.-F., Negishi, E.* A selective synthesis of a mixture of 15-epimers of (±)-11-deoxyprostaglandin E_2 methyl esters. — J. Org. Chem., 1985, **50**, N 24, 4762—4766.
55. *Lindeman, L. P., Adams, J. O.* Carbon chemical shifts for the paraffins through C9. — Anal. Chem., 1971, **43**, N 10, 1245—1253.
56. *Schneider, H.-J., Nguyen-Ba, N., Thomas, F.* Force field and ^{13}C-NMR investigations of substituted cyclopentanes. A concept for the adaption of ^{13}C NMR shifts to varying torsional arrangements in flexible compounds. — Tetrahedron, 1982, **38**, N 15, 2327—2337.
57. *Forrest, T. P., Webb, J. G. K.* Carbon-13 magnetic resonance: gamma-anti substituent effects. — Org. Magn. Reson., 1979, **12**, N 6, 371—376.
58. *Beierbeck, H., Saunders, J. K., ApSimon, J. W.* The semiempirical derivation of ^{13}C nuclear magnetic resonance chemical shifts. Hydrocarbons, alcohols, amines, ketones, and olefins. — Can. J. Chem., 1977, **55**, N 15, 2813—2828.
59. *Grant, D. M., Cheney, B. V.* Carbon-13 magnetic resonance VIII. Steric perturbation of the carbon-13 chemical shift. — J. Amer. Chem. Soc., 1967, **89**, N 21, 5315—5327.
60. *Dalling, D. K., Grant, D. M.* Carbon-13 magnetic resonance IX. The methylcyclohexanes. — J. Amer. Chem. Soc., 1967, **89**, N 25, 6612—6622.
61. *Dalling, D. K., Grant, D. M.* Carbon-13 magnetic resonance XXI. Steric interactions in the methylcyclohexanes. — J. Amer. Chem. Soc., 1972, **94**, N 15, 5318—5324.
62. *Dalling, D. K., Grant, D. M., Paul, E. G.* Carbon-13 magnetic resonance XXIII. The methyldecalins. — J. Amer. Chem. Soc., 1978, **95**, N 11, 3718—3724.
63. *Dalling, D. K., Grant, D. M.* Carbon-13 magnetic resonance XXIV. The perhydroanthracenes and perhydrophenanthrenes. — J. Amer. Chem. Soc., 1974, **96**, N 6, 1827—1834.
64. *Schneider, H.-J., Weigand, E. F.* Steric effects on carbon-13 nuclear magnetic resonance shifts in alkanes. — J. Amer. Chem. Soc., 1977, **99**, N 25, 8362—8363.
65. *Schneider, H.-J., Freitag, W.* Electric field effects on carbon-13 nuclear magnetic resonance shifts in heterosubstituted alkanes. — J. Amer. Chem. Soc., 1977, **99**, N 25, 8363—8364.
66. *Corey, E. J., Keck, G. E., Szekely, I.* Synthesis of Vane's prostaglandin X, 6,9α-oxido-9α,15α-dihydroprosta-(*Z*)5,(*E*)13-dienoic acid. — J. Amer. Chem. Soc., 1977, **99**, N 6, 2006—2008.
67. *Kotovych, G., Aarts, G. H. M.* The solution conformation of prostacyclin as determined by high field proton magnetic resonance techniques. — Can. J. Chem., 1980, **58**, N 10, 974—983.
68. *Kotovych, G., Aarts, G. H. M.* A nuclear Overhauser effect difference study of the solution conformation of (6*R*)-prostaglandin I_1. — Can. J. Chem., 1980, **58**, N 23, 2649—2659.
69. *Kotovych, G., Aarts, G. H. M., Nakashima, T. T.* A nuclear Overhauser effect study and a two-dimensional J proton magnetic resonance study of (6*S*)-prostacyclin I_1. — Can. J. Chem., 1981, **59**, N 10, 1449—1454.
70. *Kotovych, G., Aarts, G. H. M.* Application of the nuclear Overhauser effect difference experiment. Assignment of the configuration of carboprostacyclin. — Org. Magn. Reson., 1982, **18**, N 2, 77—81.
71. *Karplus, M.* Contact electron-spin coupling of nuclear magnetic moments. — J. Chem. Phys., 1959, **30**, N 1, 11—15.
72. *Karplus, M.* Vicinal proton coupling in nuclear magnetic resonance. — J. Amer. Chem. Soc., 1963, **85**, N 18, 2870—2871.
73. *Barfield, M., Karplus, M.* Valence-bond bond-order formulation for contact nuclear spin-spin coupling. — J. Amer. Chem. Soc., 1969, **91**, N 1, 1—10.
74. *Colucci, W. J., Jungk, S. J., Gandour, R. D.* An equation utilizing empirically derived substituent constants for the prediction of vicinal coupling constants in substituted ethanes. — Magn. Reson. Chem., 1985, **23**, N 5, 335—343.
75. *Pachler, K. G. R.* The dependence of vicinal proton-proton coupling constants on dihedral angle. — J. Chem. Soc. Perkin I, 1982, N 2, 1936—1940.

76. *Haasnoot, C. A., De Leeuw, F. A. A. M., Altona, C.* The relationship between proton-proton NMR coupling constants and substituent electronegativities—I. An empirical generalization of the Karplus equation. — Tetrahedron, 1980, **36**, N 19, 2783—2792.
77. *De Leeuw, F. A. A. M., Altona, C., Kessler, H., Bermel, W., Friedrich, A., Krak, G., Hull, W. E.* Conformational analysis of proline rings from proton spin-spin coupling constants and force-field calculations: application to three cyclic tripeptides. — J. Amer. Chem. Soc., 1983, **105**, N 8, 2237—2246.
78. *Kotovych, G., Aarts, G. H. M., Bigam, G.* A high-field proton magnetic resonance and nuclear Overhauser effect study of prostaglandin E_2. — Can. J. Chem., 1980, **58**, N 15, 1577—1583.
79. *Crews, P., Naylor, S., Hanke, F. J., Hogue, E. R., Kho, E., Braslau, R.* Halogen regiochemistry and substituent determination in marine monoterpenes by ^{13}C NMR. — J. Org. Chem., 1984, **49**, N 8, 1371—1377.
80. *Wiberg, K. B., Pratt, W. E., Bailey, W. F.* Nature of substituent effects in nuclear magnetic resonance spectroscopy. 1. Factor analysis of carbon-13 chemical shifts in aliphatic halides. — J. Org. Chem., 1980, **45**, N 24, 4936—4947.
81. *Stothers, J. B.* Carbon-13 NMR Spectroscopy. London, 1972, 56, 133, 143.
82. *Нярп М., Вялимяэ Т., Лопп М., Лилле Ю.* Образование трициклолактон-1,3-диоксана из лактона Грико в реакции Принса. — Изв. АН ЭССР. Хим., 1986, **35**, № 2, 157—159.

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PROSTAGLANDIINIDE ^{13}C TMR SPEKTROSKOOPIA

2. Prostanoidid hapniku aatomiga C9 juures ja nende sünteesi vaheühendid

Prostaglandiinide $F_{2\alpha}$, $F_{2\beta}$ ja E_2, prostatsükliinide I_1, I_2 ja karbatsükliini I_2 konformatsioonianalüüsi ning nende ühendite ^{13}C keemiliste nihete uurimisega on leitud sõltuvus 5-liikmelise ringi konformatsiooni ja ^{13}C nihete vahel. Selgus, et konformatsiooni muutumisega eksost endoks ehk prootonite 1,3-diaksiaalse orientatsiooni kadumisega kaasneb vastavate ^{13}C tuumade resonantssageduse nihkumine 2—3 ppm võrra tugevamasse välja. Seda sõltuvust kasutati prostanoidide sünteesi vaheühendite konformatsiooni määramiseks. Artiklis on toodud 102 prostanoidi ja nende vaheühendite ^{13}C keemilised nihked (neist 37 ühendi omad esmakordselt). Korrigeeriti mitmeid kirjanduses leiduvaid tulemusi.

Т. ВЯЛИМЯЭ, Т. ПЕХК, Э. ЛИППМАА, М. ЛОПП, Ю. ЛИЛЛЕ

СПЕКТРОСКОПИЯ ЯМР ^{13}C ПРОСТАГЛАНДИНОВ

2. Простаноиды с кислородом при С9 и промежуточные продукты их синтеза

Анализом констант спин-спинового взаимодействия $^3J_{HH'}$ и конформаций простагландинов F_2 и E_2 и ряда простациклинов установлена зависимость химических сдвигов ^{13}C в этих соединениях от конформации 5-членных циклов. Обнаружено, что исчезновение протон-протонной ориентации, близкой к 1,3-диаксиальной, сопровождается сильнопольным сдвигом резонансов соответствующих ядер ^{13}C на 2—3 м. д. Эта закономерность использована для определения конформации промежуточных продуктов синтеза простаноидов. В статье приведены химические сдвиги ^{13}C 102 простаноидов и их промежуточных продуктов.