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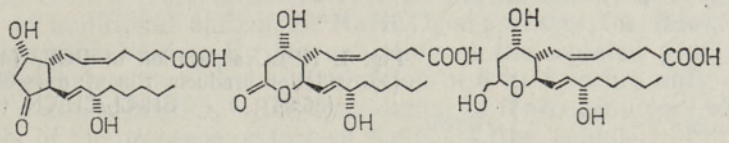
SELECTIVE BAEYER-VILLIGER OXIDATION OF β-HYDROXYKETOPROSTAGLANDINS

Introduction

The β-hydroxycyclopentanone unit present in prostaglandins (PG) of D type **1** is a structure synthetically close to thromboxanes (Tx)B **3** and especially, to an analytically useful metabolite of the latter detected in blood circulation and urine, 11-dehydro-TxB_2 **2** [1, 2].

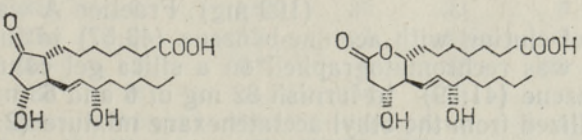


PGD_2 **1** 11-dehydro-TxB_2 **2** TxB_2 **3**

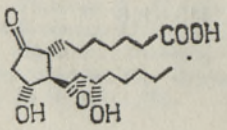
Taking into account the fact that no convenient synthesis methods have been published yet for both the above metabolites [3], we studied the direct conversion of PGD_2 to 11-dehydro-TxB_2 and further to TxB_2, using the Baeyer-Villiger oxidation followed by reduction [4]. Unfortunately, during oxidation a number of by-products, mainly epoxides, are formed [4].

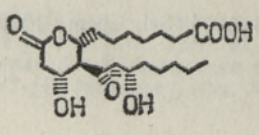
The differentiation between the Baeyer-Villiger oxidation and epoxidation reactions was achieved for a norbornenone derivative with the addition of $NaHCO_3$ and water into the reaction mixture [5]. However, this method is not suitable for synthesis of 11-dehydro-TxB_2 from PGD_2 in good yield. The relative instability of PGD_2 and 11-dehydro-TxB_2 allows no use of water and alkali in the reaction mixture [2, 6]. The efforts to oxidize PGD_2 with the other oxidants instead of *m*-chloroperbenzoic acid (MCPBA) were unsuccessful [4].

To find suitable conditions for oxidation with MCPBA, PGE_1 **1** was used as a model compound. PGE_1 is sufficiently stable and has only two reaction centers for the peracid attack.



PGE_1 **4** 8a-homooxa-PGE_1 **5**





13,14-epoxy-PGE_1 **6** 13,14-epoxy-8a-homooxa-PGE_1 **7**

In the conditions found PGD_2 was oxidized to the desired target product **2** with high yield.

Materials and methods

Materials. PGD_2 and PGE_1 were purchased from the Pilot-Production Plant of the Institute of Chemistry, Tallinn. All the other reagents were commercially available and of analytical grade. Chloroform, methylene chloride, acetonitrile and methanol were distilled before use.

HPLC. The oxidation products were separated on a 4.6×150 mm Zorbax Sil column as *p*-bromophenacyl esters of PGs. *p*-Bromophenacyl esters were prepared according to [7, 8] and detected at 254 nm (Fig. 1).

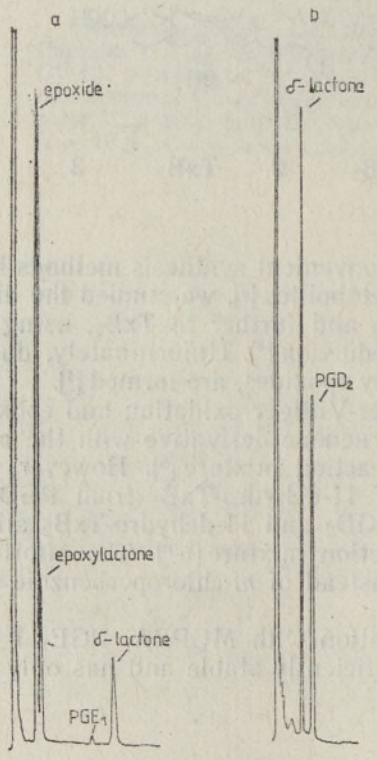


Fig. 1. HPLC separation of PGE_1 (*a*) and PGD_2 (*b*) oxidation products. Eluent: *a* — CH_2Cl_2/CH_3CN (36:64); *b* — CH_2Cl_2/CH_3CN (32:68)

Preparation of 5, 6, 7 and 2. To the cooled (−25 °C) PGE_1 solution (400 mg) in 24 ml of CH_3CN/CH_3OH (5:1) the precooled mixture of MCPBA (457 mg) in 16 ml of CH_3CN and $NaHCO_3$ (190 mg) in 16 ml of water was added by a vigorous stirring. The stirring was continued at −25 °C for 120 h. Then water (20 ml) was added and pH was adjusted to 2 with 1 N HCl. The mixture was extracted 4 times with 50 ml of chloroform and 50 ml of ethyl acetate. The extracts were combined, dried on $MgSO_4$ and evaporated. The residue consisting of **4** (0.5%), **5** (25.8%), **6** (40.4%) and **7** (32.1%) was subjected to silica gel column chromatography. The subsequent elution with chloroform-methanol (96.5:3.5, 95.5:4.5 and 80:20) gave fractions A (90 mg), B (210 mg) and C (102 mg). Fraction A was further purified on silica gel eluting with acetone-benzene (43:57) to furnish **6** (66 mg). Fraction B was rechromatographed on a silica gel column (elution with acetone-benzene (41:59) to furnish 82 mg of **6** and 68 mg of **7**. The latter was crystallized from the ethyl acetatehexane mixture (2:1) to get crystalline **7** (36 mg m. p. 95.5—97 °C). The crystallization of fraction C from the ethyl acetate-hexane solution (4:1) gave white crystals of **5** (59 mg, m. p. 125.5—129 °C).

PGD_2 (40 mg) was oxidized as described for PGE_1 using methanol instead of acetonitrile/water; evaporation of methanol in the end of the reaction (24 h) instead of extraction. **2** (12 mg) was obtained after purification on silica gel with the hexane/acetone mixture (75:25).

The structures of the isolated compounds 8a-homooxa-PGE_1 **5**, 13,14-epoxy-PGE_1 **6**, 13,14-epoxy-8a-homooxa-PGE_1 **7** and 11-dehydro-TxB_2 **2** were verified by ^{13}C NMR spectra by T. Pehk (in print).

Standard assay. The oxidation of PGE_1 and PGD_2 was performed as described above except the concentrations of PGs which were 2.5 times lower. The product composition was measured by HPLC.

The pH value. The apparent pH values in organic solutions were measured on a Laboratory Digital pH Meter OP 211/1, Radelkis, Hungary, equipped with a combined glass electrode.

Results and discussion

The oxidation of PGE_1 **4** in CH_3CN with MCPBA at room temperature or below leads mainly to epoxide **6**. In the presence of anhydrous $NaHCO_3$ the Baeyer-Villiger oxidation takes place and, in addition to **6**, compounds **5** and **7** are also formed (the Table). The addition of water to dissolve $NaHCO_3$ results in a remarkable increase in the formation of **5**. On the other hand, an additional amount of $NaHCO_3$ suppresses the Baeyer-Villiger oxidation (the Table). By the oxidation of the isolated products **5** and **6** it was clearly shown that lactonization of **6** to **7** occurs only in the presence of aqueous $NaHCO_3$ while epoxidation of **5** proceeds very slowly, independently of the presence or lack of $NaHCO_3$ (the Table).

A more detailed study of PGE_1 oxidation with MCPBA shows that the ratio of δ-lactone **5** to epoxide **6** depends on the concentration of $NaHCO_3$. A maximal of **5**/**6** ratio is achieved by adding 1 equivalent of $NaHCO_3$ (Fig. 2).

The existence of the maximum value for the **5**/**6** ratio indicates the pH dependence of the Baeyer-Villiger oxidation and double bond epoxidation reactions. The apparent pH curve for the titration of MCPBA in CH_3CN/H_2O (in the presence and absence of PGE_1) with $NaHCO_3$ gave a break between 1 to 2 equivalents of $NaHCO_3$ (Fig. 3). The apparent pH values depend on the organic solvent used. The oxidation of PGE_1 with MCPBA in methanol gave the **5**/**6** ratio about 5 times higher than that

Oxidation of 1 mg of PGE_1 (1 equiv.) with MCPBA in CH_3CN

Temp. °C	Time, h	H_2O, %	MCPBA, equiv.	$NaHCO_3$, equiv.	Product, %			
					5	**6**	**7**	**4**
20	2	—	1.5	—	—	34	2	64
20	10	—	1.5	1.6	6	36	7	51
4	20	25	2	—	—	35	5	60
4	20	25	2	1.6	27	23	6	44
4	10	25	2	3.2	12	24	3	61
4	20	25	2	0.8	—	77	23	—*
4	40	25	2	—	100	—	—	—**
4	40	25	2	1.6	99	—	1	—**

* instead of PGE_1 13,14-epoxy-PGE_1 (**6**) was used.
** instead of PGE_1 8a-homooxa-PGE_1 (**5**) was used.

in acetonitrile (Fig. 4). The optimum pH values corresponding to the maximum **5/6** ratio for CH_3OH and CH_3CN differ almost as much as the apparent pH values of similar alkali concentrations in the same solvents (1.5 pH units) (Fig. 3). From these results it appears that the Baeyer-Villiger oxidation of PGE_1 depends considerably on the apparent pH value of the reaction mixture whereas the olefin epoxidation is less influenced by it.

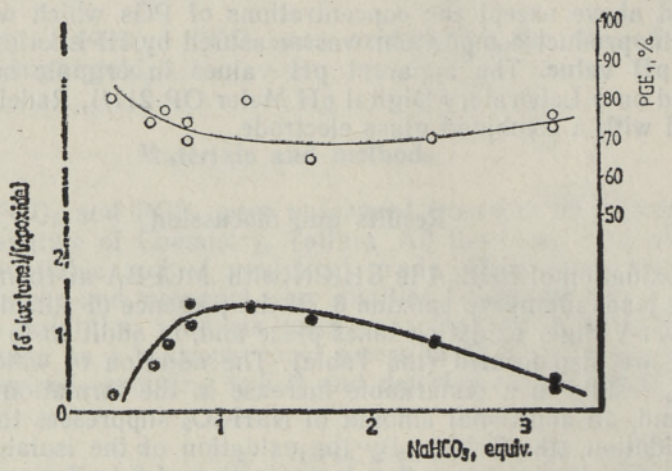


Fig. 2. Oxidation of 1 mg of PGE_1 (1 equiv.) with MCPBA (2 equiv.) in CH_3CN/H_2O (75/25) at 4 °C for 5h.

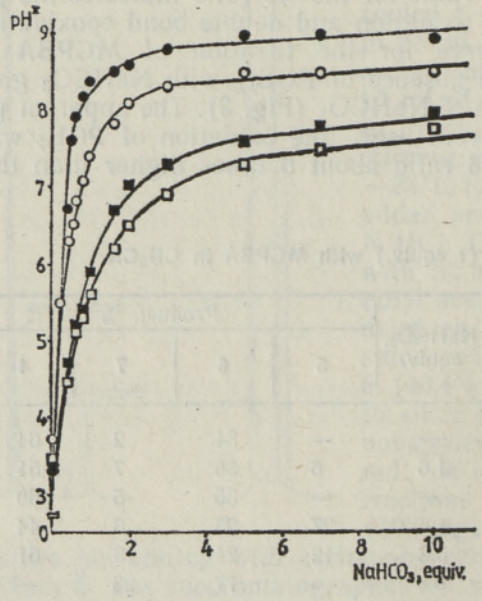


Fig. 3. Titration curve for MCPBA (2 equiv.) with $NaHCO_3$. ● — CH_3CN/H_2O (75/25) ○ — $CH_3CN/H_2O/PGE_1$ (75/25/1 equiv.), ■ — CH_3OH/H_2O (75/25 □ — $CH_3OH/H_2O/PGE_1$ (75/25/1 equiv.).

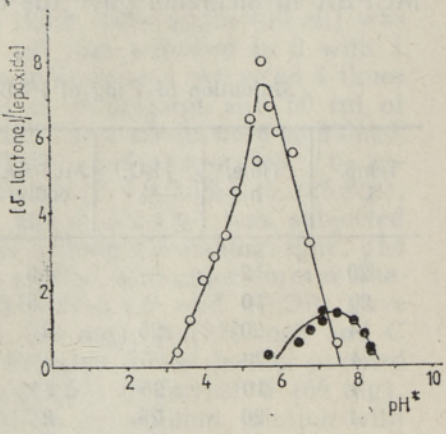


Fig. 4. Oxidation of 1 mg of PGE_1 (1 equiv.) with MCPBA (2 equiv.) at 4 °C for 5 h. The apparent pH* adjusted with $NaHCO_3$. ○ — CH_3OH/H_2O (75/25), ● — CH_3CN/H_2O (75/25)

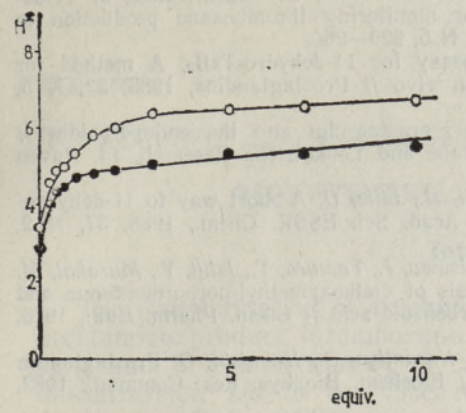


Fig. 5. Titration curve for MCPBA (2 equiv.) in CH_3OH. ○ — Na-acetate, ● — imidazole.

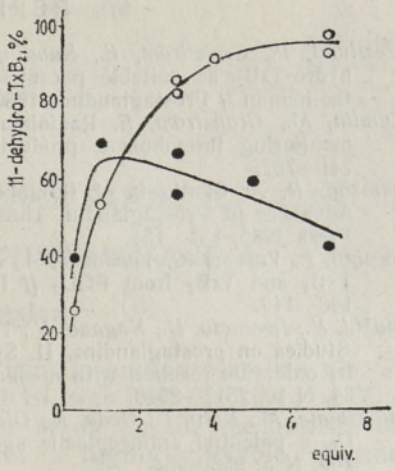


Fig. 6. Oxidation of 0.5 mg of PGD_2 (1 equiv.) with MCPBA (2.4 equiv.) in CH_3OH at −25 °C for 0.5 h. ○ — Na-acetate, ● — imidazole.

To investigate the significance of the nature of an alkali compound and the role of water in reaction medium, we buffered MCPBA with CH_3COONa and imidazole in methanol. The amounts of CH_3 COONa (1 equivalent) and imidazole (5 equivalents) were found from the titration curves (Fig. 5). A good **5/6** ratio was achieved by the oxidation of PGE_1 with MCPBA in CH_3OH in the presence of the above compounds. For example, the **5/6** ratio of 4.0 and 5.5 was achieved when pH was adjusted to 5.4 (optimum for lactonization of PGE_1 in the $CH_3OH/H_2O/NaHCO_3$ mixture) with CH_3COONa or imidazole respectively. As seen from these results, the addition of water is neccessary only in the case of $NaHCO_3$ due to its insufficient solubility in methanol and acetonitrile. The other alkali compounds whose solubility in methanol is sufficient, gave a similar ratio without additional water. Consequently, it is the solubility, not the chemical nature of alkali compound that is essential. Since water may serve a solvent component for alkali insoluble in organic solvents, the remarkable positive effect of methanol, as compared with acetonitrile, remains unclear. Probably, methanol plays an important role in the intermolecular hydrogen bond stability in peracids. It is also unclear why δ-lactone **5** remains unreacted with MCPBA to form epoxylactone **7** (the Table).

The data obtained by oxidation of PGE_1 as a model substance allow a choice of suitable reaction conditions for oxidation of PGD_2 with MCPBA. Due to the instability of PGD_2 in water [6] it is not desirable to use water solutions as reaction medium and consequently, organic solvent soluble alkali compounds should be preferred. The highest yield of **2** was achieved by 2.4 equivalents of MCPBA buffered with 7 equivalents of CH_3COONa in methanol at −25 °C (Fig. 6). Unfortunately by-products were abundantly formed during the isolation of the product from the reaction medium at room temperature. To avoid the damage of the desirable product **2**, a decrease in the excess of reagents seems to be useful and the optimum quantities experimentally found were 1.1 and 3 equivalents for MCPBA and CH_3COONa, respectively.

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β-HÜDROKSÜKETOPROSTAGLANDIINIDE SELEKTIIVNE OKSÜDATSIOON BAEYERI-VILLIGERI JÄRGI

On leitud lihtne meetod tromboksaanide ja nende analoogide sünteesiks, oksüdeerides β-hüdroksüketoprostaglandiine Baeyeri-Villigeri järgi perhapetega. Laktooni saagise suurendamiseks ja kõrvalühendi — epoksiidi tekke vältimiseks on optimeeritud reaktsioonitingimused, kasutades mudelühendina PGE_1. Oksüdatsiooniproduktid on eraldatud ja identifitseeritud ning leitud, et laktooni ja epoksiidi suhe sõltub oluliselt lahustist, näiva pH väärtusest ja temperatuurist. Optimaalsetel tingimustel metanoolis näiva pH 5,6 juures −25 °C on 11-dehüdro-TxB_2 saagis kuni 98%.

Ивар ЯРВИНГ, Айно ВАХЕМЕТС, Кюллики ВАРВАС, Нигулас САМЕЛЬ, Юло ЛИЛЛЕ

СЕЛЕКТИВНОЕ ОКИСЛЕНИЕ β-ГИДРОКСИКЕТОПРОСТАГЛАНДИНОВ ПО БАЙЕРУ—ВИЛЛИГЕРУ

Разработан простой метод синтеза тромбоксанов и их аналогов с помощью окисления по Байеру—Виллигеру β-гидроксикетопростагландинов органическими перкислотами. Для повышения выхода δ-лактона и предотвращения образования побочного продукта — эпоксида — оптимизированы условия реакции при использовании в качестве модельного соединения $ПГЕ_1$. Продукты окисления выделяли и идентифицировали. Найдено, что отношение лактон/эпоксид сильно зависит от кажущейся величины pH среды, температуры и растворителя. Показано, что выход 11-дегидро-TxB_2 в метаноле при кажущейся величине pH 5,6 при —25° С достигает 98%.