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AN APPROACH TO THE SYNTHESIS OF 5-AZAPROSTACYCLIN[1]

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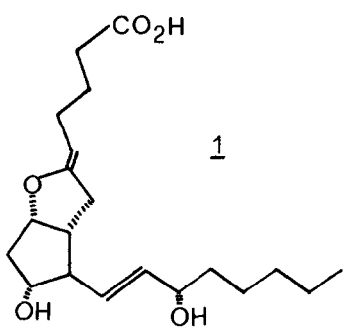
Abstract: The synthesis of a biologically active 5-azaprostacyclin as well as some of its chemical properties are described.

Due to the inherent chemical instability of natural prostacyclin (PGI_2) 1 there is a great interest in obtaining chemically stable prostacyclin analogs with the same or modified biological profile as PGI_2. Several groups have obtained chemically stable PGI_2-analogs by replacing the enol ether oxygen in 1 by a sulfur or nitrogen atom[2] as well as by a methylene group[3].

In this paper is described the synthesis of the optically active 5-azaprostacyclin-derivative 3 in which the enol ether system has been replaced by an imino ether moiety. Only a few examples of exocyclic 2-iminotetrahydrofurans have appeared in the literature. These have been usually obtained from ω-hydroxy-nitriles or unsaturated nitriles[4], from the cyclization of ω-halo amides or the condensation of primary amines with 2,2-diethoxytetrahydrofuran[5]. Attempts to cyclize the nitrile 4[6] and alkylate the intermediate with ethyl 4-bromobutyrate were not successful. It therefore became necessary to devise another approach for the preparation of 5-azaprostacyclin.



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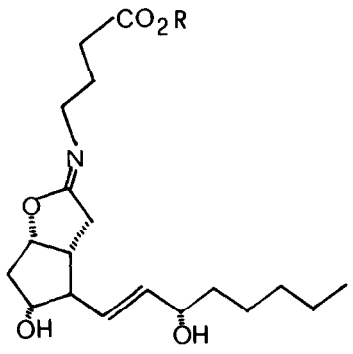


2 R=H
3 R=C_2H_5

The readily available acid 5[7] was converted into the mixed anhydride (Et_3N, $ClCO_2$-i-Bu) and reacted with ethyl 4-aminobutyrate to afford the amine 6 which gave with n-Bu_4NF-THF the alcohol 7 in 75 % yield. Alternatively, 7 was obtained by heating 8[8] with ethyl 4-aminobutyrate in the presence of 2-hydroxypyridine[9] (86 % yield). Mesylation of 7 (CH_3SO_2Cl-pyridine, 20 h, 0°C) to 9[10] followed by removal of the tetrahydropyranyl ethers (60 % CH_3CO_2H, 18h, 20°C) gave crystalline 10[11] (81 % yield from 7). Ring-closure to 3 was achieved by a double inversion technique. Thus 10 was treated with LiBr-$NaHCO_3$ in DMF at 60°C for 17 hours to furnish a mixture of 3 and 11, the separation of which was a decisive step. Partitition between 0.1 M citrate buffer (pH 4) and ether-dichloromethane (4 : 1) gave 11[12] (30 %) from the organic layer. The aqueous layer afforded an treatment with Na_2CO_3 (pH 8) and extraction with dichloromethane crystalline 3[13] (51 %).

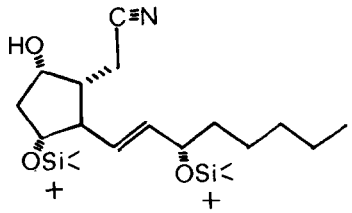
The ^{1}H-NMR-spectrum of 3[13] indicated the presence of a single isomer. Since a protonated imino species is involved in the purification step one can assume that the thermodynamically more favoured Z-isomer is formed. This is supported by MNDO-calculations which show the Z-isomer to be more stable as indicated by an energy difference of 17 kJ·mol^{-1} between E- and Z-isomer.[14]

The imino ether 3 can be stored for several months at 4°C without decomposition and an increased stability towards hydrolytic conditions was observed when compared with 1-methylester. The half life of 3 in aqueous solution is 11.5, 33 and 72 hours at a pH of 4.5, 7 and 8 respectively.[15]

Attempts to obtain the acid 2 by saponification of the ethyl ester 3 under basic or neutral (lipase)[16] conditions resulted in the formation of 12 and 13. This is probably due to internal protonation of the imino ether nitrogen by the carboxyl group followed by rapid addition of water and ring cleavage.

In the rat, 3 (1 mg/kg p.o.) caused a 17 % decrease of the systolic blood pressure lasting for 60 minutes, however no effect was observed on blood platelet (rat or human) aggregation. Further biological properties of this azaprostacyclin are being presently investigated.

Acknowledgement. The author thanks Prof. H. Vorbrüggen for stimulating discussions and Dr. D. Rosenberg for the interpretation of NMR-data, Dr. J. Casals-Stenzel and Dr. M. Town for providing the biological data, and Mr. G. Neumann for technical assistance.



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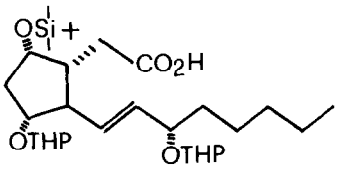

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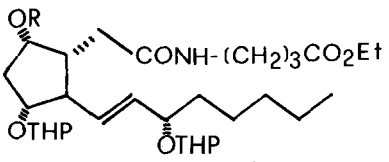
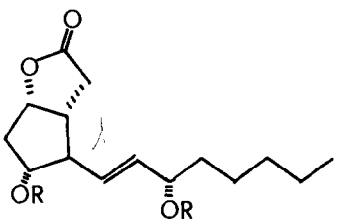


6 R = Si +

7 R = H

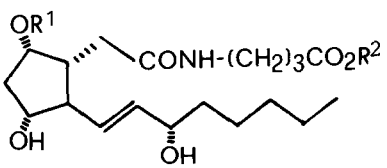
9 R = SO_2CH_3



8 R = THP

12 R = H

14 R = Si +



10 $R^1 = SO_2CH_3$ $R^2 = Et$

11 $R^1 = H$ $R^2 = Et$

13 $R^1 = H$ $R^2 = H$

References and Notes

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2) W. Bartmann and G. Beck, Angew. Chem. 94, 767 (1982).

3) See, for example: W. Skuballa, H. Vorbrüggen, Angew. Chem., Int. Ed. Engl. 20, 1046 (1981); K.C. Nicolaou, Chem. Commun. 1067 (1978); Y. Konishi, M. Kawamura, Y. Arai, M. Hayashi, Chem. Lett. 1437 (1979).

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b: T. Mukaiyama, K. Sato, Bull. Chem. Soc. Jap. 36, 99 (1963).

6) 4 was obtained by reduction of 14 with diisobutylaluminum hydride, reaction of the corresponding lactol with hydroxylamine hydrochloride in pyridine and dehydration of the aldoxime with $TiCl_4$/pyridine. For the dehydration procedure see W. Lehnert, Tetrahedron Lett. 559 (1971).

7) D.R. Morton and J.L Thompson, J. Org. Chem. 43, 2102 (1978).

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9) H.T. Openshaw, N. Whittaker, J. Chem. Soc., (C) 89 (1969).

10) 9, oil; IR ($CHCl_3$): 3443, 2933, 2860, 1725, 1661, 1518, 1352, 1168, 1017, 972, 907 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.90 (3H,t,J = 7 Hz), 1.32 (3H,t,J = 7 Hz), 2.39 (2H,t,J = 6.5 Hz), 3.01 (3H,s), 3.25 (2H,ABq,J = 16 Hz), 4.11 (2H,q,J = 7 Hz), 4.55 (2H,m), 5.07 (1H,m), 5.38 (1H, dd,J = 8+15 Hz), 5.52 (1H,dd,J = 7+15 Hz), 5.90 (1H,t,J = 6.5 Hz).

11) 10, mp. 79-81°C; IR ($CHCl_3$): 3605, 3440, 2928, 1727, 1662, 1518, 1350, 1169, 1030, 971, 908 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.88 (3H,t,J = 7 Hz), 1.24 (3H,t,J = 7 Hz), 2.30 (2H,t,J = 6.5 Hz), 3.03 (3H,s), 3.25 (2H,ABq,J = 16 Hz), 4.10 (2H,q,J = 7 Hz), 5.06 (1H,m), 5.40-5.61 (2H,m), 6.09 (1H,t,J = 6 Hz).

12) 11, oil; IR ($CHCl_3$): 3602, 3442, 2930, 2859, 1728, 1651, 1521, 972 cm^{-1}.

13) 3, mp. 86-88°C; $[\alpha]_D$= +33,3° (c = 1 in $CHCl_3$); IR ($CHCl_3$): 3600, 3390 br., 2931, 1725 sh, 1701, 1163, 1085, 1029, 970, 903 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.88 (3H,t,J = 6 Hz), 1.22 (3H,t, J = 7 Hz), 1.26-1.58 (8H,m), 1.71-1.90 (4H,m), 2.12 (1H,dd,J = 8.5+18 Hz), 2.32 (2H,t,J = 7Hz), 2.52 (1H,dd,J = 7.5+15 Hz), 2.66 (1H,dd,J = 9.5+17 Hz), 3.07-3.31 (2H,m), 3.85 (1H, dd,J = 8+17.5 Hz), 3.99 (1H,t,J = 6.5 Hz), 4.08 (2H,q,J = 7 Hz), 4.69 (1H,dt,J = 2.5+6.5 Hz), 5.45 (1H,dd,J = 8+15 Hz), 5.58 (1H,dd,J = 6.5+15 Hz).

14) I am obliged to Dr. C. Herrmann for the MNDO-calculations.

15) The half life of 1-methylester at physiological pH has been determined to be 4.5-6 hours, see: Y. Chiang, A.J. Kresge, M.J. Cho, J. Chem. Soc. Chem. Commun. 129 (1979). The chemical stability of 1 has also been reported by M.J. Cho and M.A. Allen, Prostaglandins 15,943 (1978).

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