PROSTAGLANDIN ANALOGUES; THE SYNTHESIS OF NEW THROMBOXANE DERIVATIVES FROM NATURAL SAFROLE[1]

FERNANDO A.S. COELHO, PAULO R.R. COSTA,* FLORENCE M.C. de FARIAS, ELIEZER BARREIRO§*

Núcleo de Pesquisas de Produtos Naturais* and Faculdade de Farmácia,§ Universidade Federal do Rio de Janeiro, C.C.S., Bloco H, 2194l, Rio de Janeiro, R.J., Brazil

Recebido em 26/01/84

ABSTRACT: A new class of aromatic compounds (2,3) posseding mixed structural features of thromboxane (Tx) and non-steroid anti-inflammatory agents (NSAIA) was synthesized using natural safrole (1) as starting material.

As part of an ongoing research program aiming at the synthesis of biologically attractive compounds from Brazilian abundant natural products, we became interested in synthesizing aromatic compounds with both structural features of Tx's and NSAIA's.

It is now well established that prostaglandins (PG) and other compounds biosynthesized from arachidonic acid cascate are involved in the inflammatory process.[2] While PG biosynthesis is a complex, multistep process, the main step concerning the NSAIA is the initial step - substrate binding by ciclooxygenase (CO)- which is inhibited by the NSAIA's members of the arylacetic and arylpropionic acids class.[3]

In a previous report we synthesized NSAIA related to indomethacin using natural safrole (1) as starting material,[4] and in the present study we describe the synthesis of compounds 2-3 having both structural requirements for NSAIA's and Tx-analogues using as starting material this abundant, easily accessible natural product.

The synthesis of the Tx-analogue 2 is ilustrated in Scheme 1. Ozonolysis of 1, isolated from sassafraz oil, gave homopiperonal 4 in 80% yield.[4] The most efficient process to introduce the appropriate functionalization at the activated 6-ring position was found to be the Bouveault reaction[5] on the dimethyl ketal bromide 5.[6] This intermediate was preparated in 95% yield, in one step sequence, by treatment of a methanolic solution of 4 with bromine in presence of a catalytic ammount of 2,2-dimethoxy propane.[7] Introduction of the formyl unit was next accomplished by treatment of an ethereal solution of 5 with butyllithium followed by dry dimethylformamide (DMF)to give the mono protected dialdehyde 6 in 89% yield. The completion of the w-chain of 2 was achieved by first subjecting the aldehyde 6 to an Emmons Horner reaction with dimethyl (2-oxoheptyl) phosphonate,which produced the enone 7 in 75% yield. The acetic acid chain in 9 was obtained by acidic treatment of 7 in order to deblock the aldehyde moiety, followed by Jones oxidation of the aldehyde-enone 8. Finally, the target compound 2 was prepared by 1,2-reduction of the ketone-acid 9 by using sodium borohydride in methanol.

The synthesis of the tetranor Tx-analogue 3 is illustrated in Scheme 2. Thus, regioselective oxidation at the terminal carbon of the allyl unit of 1 was achieved by using the sequence hydroboration-oxidation. In this way, treatment of safrole (1) with diborane, generated *in situ*, followed by careful treatment with H_2O_2 gave very cleanly the primary alcohol 10, in 55% yielde .[8] Jones oxidation of an acetone solution of 10 furnished quantitatively the desired propionic acid 11. Finally, the synthesis of 3 was completed by application, again successfully, of the w-chain introduction procedure on the ester aldehyde 12, obtained in high yield by using conventional methodology.[8a]

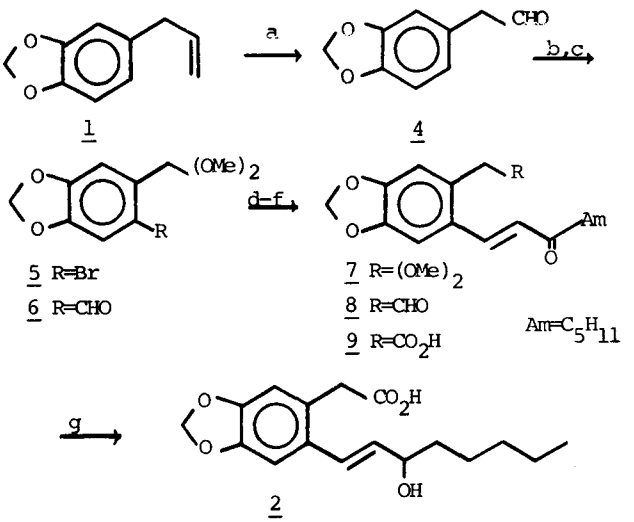
In conclusion, these new Tx-analogues 2 and 3, which may be considered as mixed compounds of Tx and NSAIA with potential Tx-antagonist activity, were obtained from natural safrole in 64% and 56% overall yield respectively.

ACKNOWLEDGMENT: The authors thanks CNPq by financial support (40.1037/82) and for fellowships to FASC, FMCF. Partial financial support from CEPG-UFRJ is also achnowledged.

REFERENCES:

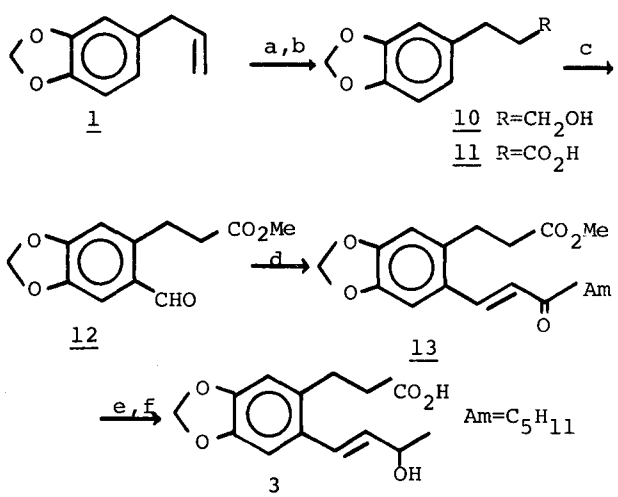
1. Paper 6 in the serie "Synthesis of Biologically Active Compounds from Abundant Natural Products", for previous paper in this series, see: L.N.F.L. Gomes and E.J. Barreiro, J. Chem. Res.(S) 1983, 000; (M) 1983, 0000.
2. S.H. Ferreira, S. Moncada and J.R. Vane, Nature, New Biology 1971, 231, 237; S.H. Ferreira and J.R. Vane, Ann. Rev. Pharmacol. 1974, 23, 1439.
3. T.Y. Shen, E.A. Ham, V.S. Cirillo and M. Zanetti in "Prostaglandin Synthetade Inhibitors", J.R. Vane and H.R. Robinson, Eds., Haven Press, New York, 1974, p. 19.
4. E.J. Barreiro, P.R.R. Costa, P.R.V.R. Barros and W. M. Queiroz, J. Chem. Res.(S) 1982, 102, (M) 1982 1142.
5. D.C. Owsley, J.M. Nelke and J.J. Bloomfield, J.Org. Chem. 1973, 38, 901; see also: C. Petrier, A.L. Gemal and J.L. Luche, Tetrahedron Lett. 1982, 23, 3361.
6. All new compounds reported herein shown PMR, IR and MS data in accord with the proposed structure.
7. F.A.S. Coelho, M.Sc. Thesis, Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, 1983.
8. a) F.M.C. de Farias, P.R.R. Costa and E.J. Barreiro, unpublished results; b) cf. H.C. Brown, S. Kulkarni and C.G. Rao, Synthesis 1980, 151.

SCHEME I



a) O_3-O_2, AcOH, 0°C; Zn (powder), 0°C, 4h (80%); b) Br_2, MeOH, 2,2-DMP, 0°C (95%); c) n-BuLi (2.0 eq.), Et_2O, -78°C, 1h; DMF (2.0 eq.), Et_2O, -78°C-rt, 12 h (89%); d) $(Meo)_2POCH_2COAm$, NaH, DME, rt, 12h(75%); e) 15% aq. H_2SO_4, Me_2CO, rt, 2h (99%); f) CrO_3,H_2SO_4, Me_2CO 0°-5°C (86%); g) $NaBH_4$, MeOH -15°C (85%).

SCHEME 2



a) NaBH, BF_3O, diglime, 20°C, 1h; 30% H_2O_2, 6N NaOH, reflux, 4h (55%); b) CrO_3, H_2SO_4, Me_2CO, 0°-5°C (75%); c) reference 7; d) $(MeO)_2POCH_2$-COAm, KH, DME, rt, 12h (75%); e) $NaBH_4$, MeOH, -15°C (85%); f) K_2CO_3 MeOH:H_2O (4:1), rt, 12h (98%).