Tetrahedron Letters No. 34, pp 2931 - 2934, 1975. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 11-DESOXY-8-AZAPROSTAGLANDIN E_1[1]

George Bolliger and Joseph M. Muchowski*

Research Laboratories, Syntex, S. A., Apartado Postal 10-820, Mexico 10, D. F.

(Received in USA 9 May 1975; received in UK for publication 10 July 1975)

The synthesis of analogues of the naturally occurring prostaglandins has, during the past few years, been occupying the interest of a constantly increasing number of investigators. The great majority of these studies have centered on various modifications of the two side chains, or of the substitution pattern of the 5-membered carbocyclic system present in the natural prostanoids[2,3]. An examination of the effect, on the biological activity, of the introduction of heteroatoms into the 5-membered ring has, however, recently commenced, and several series of heterocyclic prostaglandins {the 9-oxa[4], 10-oxa[5,6], 11-oxa[7-9], 9,11-dioxa[10], 9-thia[11], 11-thia[12], and 8,12-diaza[13] series} have now been reported. This publication describes the synthesis of the title compound, which is believed to be the first known monoaza prostaglandin.

The sodium salt of the known[14] L (+) methyl pyroglutamate (1) was alkylated with methyl-7-bromoheptanoate, and the racemic diester (2a)[15] thus obtained, was, as expected[16], selectively hydrolysed to the half acid (2b; 75% from 1) {oil; ν_{max} 1735, 1690, 1650 cm^{-1}} with aqueous methanolic potassium carbonate. This acid was reduced[17], via the mixed methyl carbonic-carboxylic anhydride, to the primary alcohol (3) {m.p. 54°; ν_{max} 3640, 3390, 1735, 1670 cm^{-1}; m/e 257 (M^+), 226 (M-CH_2OH), 194 (M-CH_2OH-CH_3OH)} with aqueous sodium borohydride (70-75% yield). Oxidation of the alcohol with Collins reagent[18] gave the unstable aldehyde (4) {oil; ν_{max} 2710, 1735, 1685 cm^{-1}; n.m.r. 9.45 p.p.m. (d, J = 3, CHO)} which was condensed, without purification, with the sodium salt of dimethyl-2-oxoheptylphosphonate. The enone (5; 60-65% from 3) {oil; λ_{max} 216 nm

(log ε 4.10); m/e 351 (M^+), 252 ($M-C_5H_{11}CO$)} was reduced with zinc borohydride in dimethoxyethane to give a 1:1 mixture (88%) of alcohols epimeric at C-15. This mixture was separated by preparative t.l.c. on silica gel using a benzene: ether:methanol (100:40:7) solvent system, into the more polar (6a) {oil ν_{max} 3620, 3440, 1735, 1670 cm^{-1}; n.m.r. 3.63 (s, OCH_3), 4.10 (m, 15-CH), 5.46 (q, $J_{13,14}$ = 15.3, $J_{12,13}$ = 7.6, 13-CH), 5.72 (q, $J_{13,14}$ = 15.3, $J_{14,15}$ = 5.6, 14-CH); m/e 353 (M^+)} and a less polar isomer (7a) {spectral data very similar to (6a)}.

The α-configuration was assigned to the more polar isomer by analogy with the chromatographic behaviour of the esters of the natural prostaglandins, as well as on the basis of the chemical shift of carbon-13 in the ^{13}C n.m.r. spectrum. The resonance of carbon-13 for the α-isomer appeared at a lower field (130.23 p.p.m.) than did the corresponding carbon in the β-epimer (129.88 p.p.m.). Similar chemical shift differences have been observed[19,20] for a considerable number of pairs of prostaglandins epimeric at C-15.

The esters were saponified with one equivalent of sodium hydroxide in boiling aqueous methanol. The higher melting α-acid (6b) {m.p. 109°; ν_{max} 3620, 1715, 1670 cm^{-1}; m/e 339 (M^+), 321 ($M-H_2O$), 268 ($M-C_5H_{11}$), 238 ($M-C_5H_{11}CHOH$), 224 ($M-(CH_2)_5COOH$)} was more active in several biological assays than was the corresponding β-epimer (7b) {m.p. 90°, spectral data similar to (6b)}[21].

The complete preparative details and physical properties for the compounds described herein, as well as for those of several closely related derivatives, will be published in the full paper.

REFERENCES

1. Contribution No. 453 from the Syntex Institute of Organic Chemistry.

2. U. Axen, J.E. Pike, and W.P. Schneider, Synthesis, Vol. 1, Ed. by J.W. ApSimon, John Wiley and Sons Inc., New York, N. Y., 1973, pp. 118-138.

3. P.H. Bently, Chem. Soc. Reviews, 2, 29 (1973).

4. I. Vlattas and L. DellaVecchia, Tetrahedron Letters, 4455 (1974).

5. J. Himizu, S. Harigaya, A. Ishida, K. Yoshikawa, and S. Masanari, Ger. Offen. 2,229,225 (1972); Chem. Abstr., 78, 111, 102q (1973).

6. F.M. Hauser and R.C. Huffman, Tetrahedron Letters, 905 (1974).

7. I.T. Harrison, V.R. Fletcher, and J.H. Fried, Tetrahedron Letters, 2733 (1974).

8. S. Hanessian, P. Dextraze, A. Fougerousse, and Y. Guindon, Tetrahedron Letters, 3983 (1974).

9. I. Vlattas and A.O. Lee, Tetrahedron Letters, 4451 (1974).

10. I.T. Harrison and V.R. Fletcher, Tetrahedron Letters, 2729 (1974).

11. I. Vlattas and L. DellaVecchia, Tetrahedron Letters, 4267, 4459 (1974).

12. I.T. Harrison, R. Taylor, and J.H. Fried, Tetrahedron Letters, 1165 (1975)

13. R.M. Scribner, Ger. Offen. 2,323,193 (1973); Chem. Abstr., 80, 47, 986t (1974).

14. E. Fischer and R. Boehner, Chem. Ber., 44, 1332 (1911).

15. All new compounds described herein were fully characterized.

16. F.W. Foreman, Biochem. J., 8, 32 (1914).

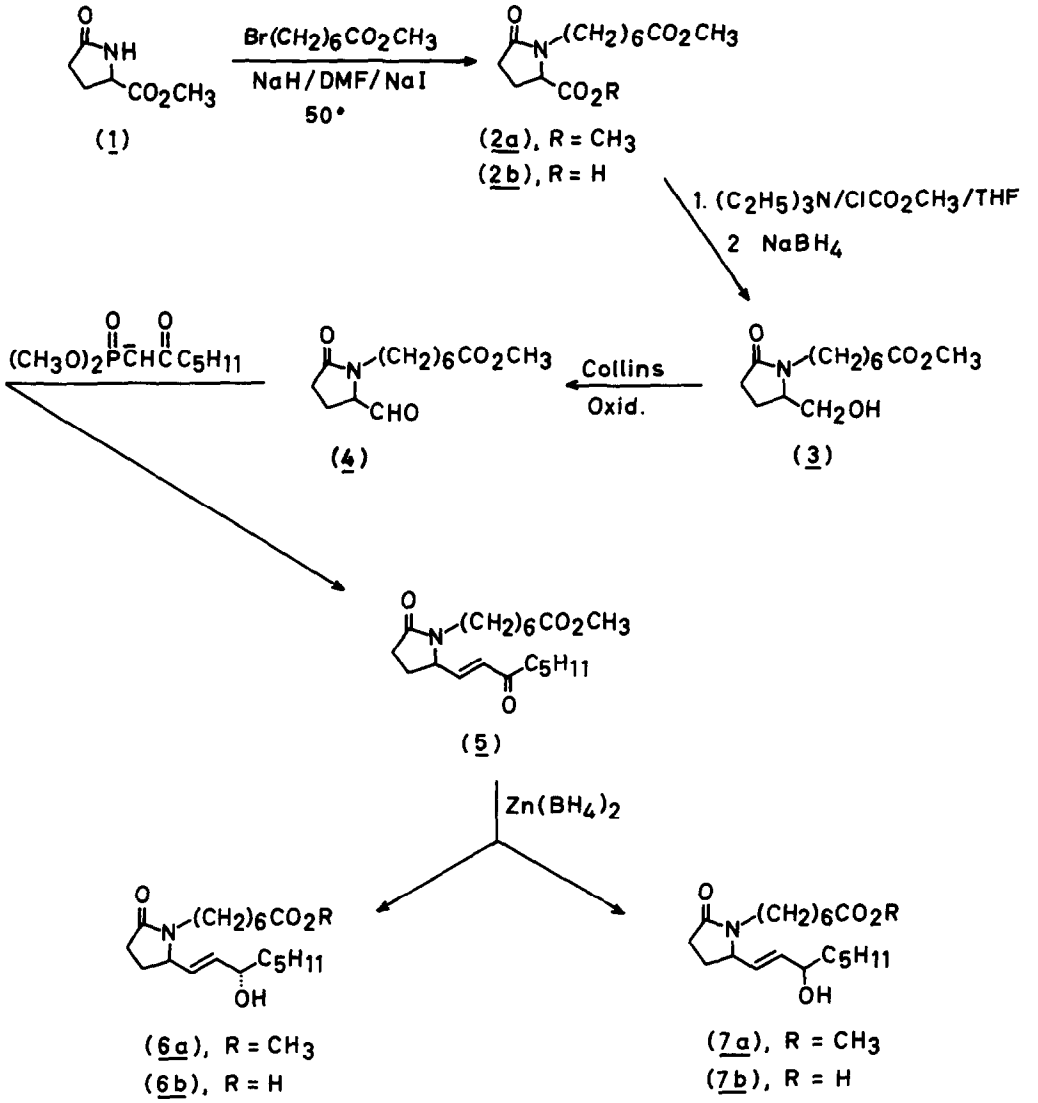
17. K. Ishizumi, K. Koga, and S.I. Yamada, Chem. Pharm. Bull., 16, 492 (1968).

18. J.C. Collins, W.W. Hess, and F.J. Frank, Tetrahedron Letters, 3363 (1968).

19. G.F. Cooper and J. Fried, Proc. Nat. Acad. Sci. U. S. A., 70, 1579 (1973).

20. M.L. Maddox, Syntex Research, Palo Alto, Calif. Unpublished observations.

21. We thank W. Rooks for this data.


Br(CH2)6CO2CH3
NaH/DMF/NaI
50°
(1)
(2a), R = CH3
(2b), R = H
1. (C2H5)3N/ClCO2CH3/THF
2 NaBH4
(3)
Collins
Oxid.
(4)
(CH3O)2PCHCC5H11
(5)
Zn(BH4)2
(6a), R = CH3
(6b), R = H
(7a), R = CH3
(7b), R = H