Tetrahedron Letters No. 35, pp 3335 - 3338.

0040-4039/79/0822-3335$02.00/0

8,10,12-TRIAZAPROSTAGLANDIN ANALOGUES

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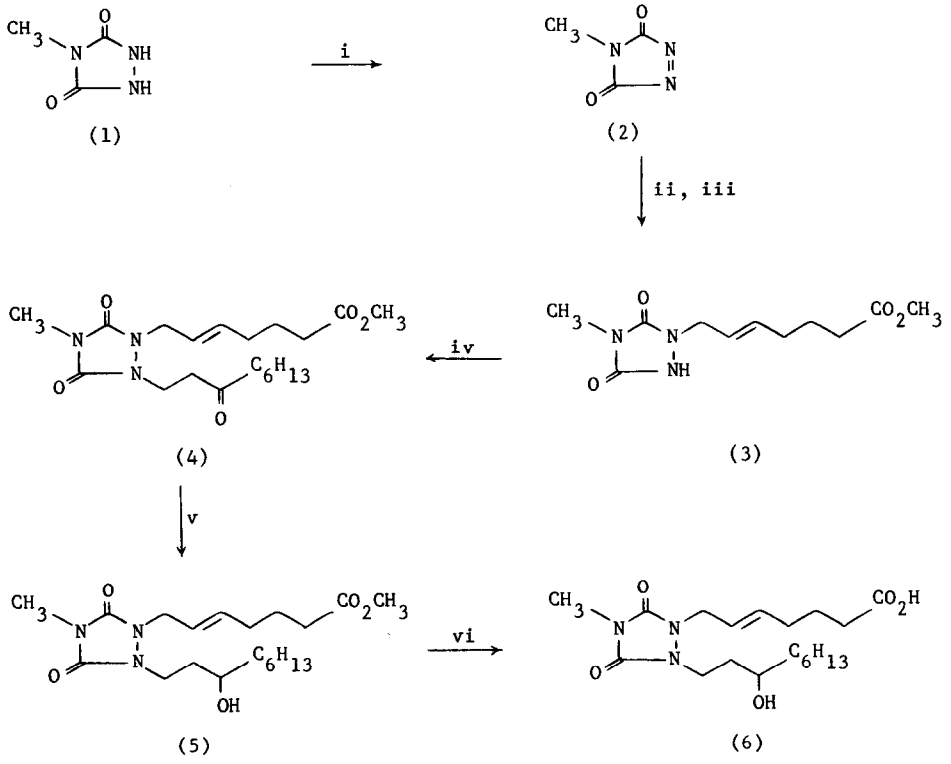
Abstract: A versatile synthetic procedure for the preparation of 8,10,12-triazaprostaglandin analogues is described.

We have previously indicated our interest in azaprostaglandins[1,2] and have found that 12-aza-[1] and 10,12-diaza-[3] prostaglandin analogues retain much of the biological activity shown by the natural prostaglandins[4]. In this preliminary communication we report a versatile synthetic procedure for the preparation of 8,10,12-triazaprostaglandin analogues (see Schemes 1 and 2).

Scheme 1



Reagents: i; N_2O_4, CH_2Cl_2, Na_2SO_4, 0°, 1 hr.

ii; $CH_2=CH(CH_2)_4CO_2H$, C_6H_6, reflux, 1 hr.

iii; H^+, CH_3OH, reflux, 5 hrs.

iv; $CH_2=CHCOC_6H_{13}$, benzyltrimethyl ammonium hydroxide, dioxane, reflux, 3 hr.

v; $NaBH_4$

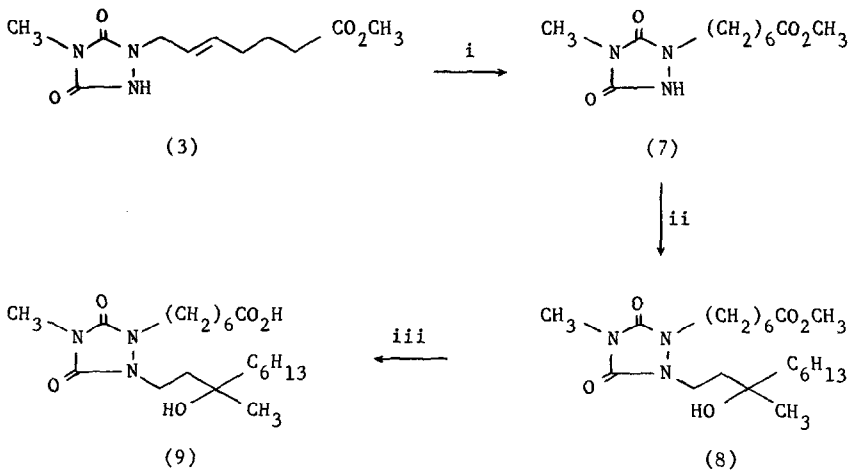
vi; 10% aq. Na_2CO_3 in CH_3OH, reflux, 18 hr.

4-Methyl-1,2,4-triazolidine-3,5-dione (1) was prepared according to Deucker and Zinner[5]. Oxidation of (1) to the triazoline dione (2) was accomplished with dinitrogen tetroxide[6] and, without purification, (2) was subjected to an 'ene' reaction with hept-6-enoic acid[7] in refluxing benzene. Esterification and subsequent purification[8] gave the trans[9] triazolidine dione (3) in 40% yield[10] based on (1). [M.p. 55-7°. I.R.: ν_{max} (melt), 1760, 1670-1740 cm^{-1}. NMR[11]: τ($CDCl_3$), 1.05-2.0 (brs, 1H, NH); 4.20 (sx, 1H, J = 15, 6, 6Hz, $NCH_2CH=C\underline{H}$); 4.52 (sx, 1H, J = 15, 6, 6 Hz, $NCH_2C\underline{H}=CH$); 5.95 (brd, 2H, NCH_2); 6.34 (s, 3H, CO_2CH_3); 6.95 ppm (s, 3H, NCH_3). $C_{11}H_{17}N_3O_4$ requires C, 51.76; H, 6.71; N, 16.46%; m/e (m*) 255.1219: found C, 51.55; H, 6.56; N, 16.59%; m/e (m*) 255.1243].

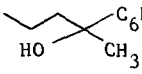
Michael addition of non-1-en-3-one[12] to the triazolidine dione (3) in refluxing dioxane in the presence of benzyltrimethyl ammonium hydroxide gave (4) which was subsequently reduced with sodium borohydride to give the triazolidine dione (5) as an oil in 76% yield after purification . [Mass spectrum: m/e (m*) requires 397.2591; found 397.2582]. Hydrolysis of (5) with aqueous sodium carbonate in methanol gave the required 8,10,12-triazaprostaglandin analogue (6) as a viscous oil. [I.R.: ν_{max} (film), 2500-3600, 1640-1780 cm^{-1}. NMR: τ ($CDCl_3$), 3.9 (s, 2H, OH, CO_2H) overlapped with 4.4 (m, 2H, $C\underline{H}=C\underline{H}$, only J = 15 Hz visible); 5.8 (brt, 2H, $NC\underline{H}_2CH=CH$); 6.0-6.7 (brm, 3H, NCH_2, $C\underline{H}OH$); 6.9 (s, 3H, NCH_3); 9.1 ppm (brt, 3H, $(CH_2)_5C\underline{H}_3$). $C_{19}H_{33}N_3O_5$ requires C, 59.51; H, 8.67; N, 10.96%: found C, 59.04; H, 8.71; N, 10.70%].

In an attempt to circumvent the known 15-dehydrogenase deactivation of prostaglandins[4] a series of 15-methyl substituted compounds were also prepared (Scheme 2).

Scheme 2



Reagents: i; H_2, 10% Pd/C, DME

ii; TsO  , Na_2CO_3, NaI, HMPA, RT, 7 days

iii; 10% aq. Na_2CO_3 in CH_3OH, reflux, 18 hrs.

Hydrogenation of (3) afforded the saturated triazolidine dione (7) [M.p. 80-1°. Mass spectrum: m/e (m*) requires 257.1375; found 257.1377] which was alkylated with 1-(toluene-p-sulphonyloxy)-3-methylnonan-3-ol[13] to give (8) as an oil after purification by chromatography. [I.R.: ν_{max} (film), 3500, 1770, 1680-1740 cm^{-1}. NMR: τ($CDCl_3$), 6.15-6.6 (brm, 4H, 2 x NCH_2); 6.35 (s, 3H, CO_2CH_3); 7.0 (s, 3H, NCH_3); 7.5-7.8 (m, 3H, $CH_2CO_2CH_3$, OH); 9.1 ppm (brt, 3H, $(CH_2)_5CH_3$). $C_{21}H_{39}N_3O_5$ requires C, 60.99; H, 9.51; N, 10.16%; m/e (m*) 413.2769: found C, 60.51; H, 9.72; N, 10.05%; m/e (m*) 413.2829]. Alkaline hydrolysis of (8) gave the required 8,10,12-triazaprostaglandin analogue (9) as a viscous oil which solidified on standing. [M.p. 52-4°. I.R.: ν_{max} (Nujol), 2500-3500, 1770, 1680-1740 cm^{-1}. NMR: τ(DMSO), 6.2-6.7 (brm, 4H, 2 x NCH_2); 7.1 (s, 3H, NCH_3); 7.8 (brt, 2H, CH_2CO_2H); 9.1 ppm (brt, 3H, $(CH_2)_5CH_3$). $C_{20}H_{37}N_3O_5$ requires C, 60.13; H, 9.33; N, 10.52%; m/e (m*) 399.2734: found C, 59.61; H, 9.57; N, 10.38%; m/e (m*) 399.2688].

The unsaturated analogue of (8) can be prepared by alkylation of the triazolidine dione (3) with the tosylate (reagent ii) followed by purification on column chromatography.

The 8,10,12-triazaprostaglandin analogues were isolated as racemic mixtures and were screened as such for biological activity. The bronchodilation activity of these analogues will be reported elsewhere[14].

References and Notes

1. Belgian Patent BE 835 989 (1976).

2. F. Cassidy and G. Wootton, Tetrahedron Letters, 1525 (1979).

3. West German Patent DT 2755771 (1978).

4. See for example, Advances in Prostaglandin Research, Volumes 1 and 2, Ed. B. Samuelsson and R. Paoletti, Raven Press, 1976.

5. G. Zinner and W. Deucker, Arch. Pharm., 294, 370 (1961).

6. J.E. Herweh and R.M. Fantazier, Tetrahedron Letters, 2101 (1973).

7. E.A. Braude, R.P. Linstead and K.R.H. Wooldridge, J. Chem. Soc., 3074 (1956).

8. Purification was carried out by column chromatography using Merck Kieselgel 60 with chloroform and chloroform:ethanol as eluants.

9. The trans stereochemistry of compound (3) was verified by irradiation at τ5.95 when the signal at τ4.52 collapsed to a doublet of coupling constant J = 15 Hz, and by irradiation at τ7.91 causing the signal at τ4.20 to collapse to a doublet of coupling constant J = 15 Hz. G. Stork and G. Kraus, J. Amer. Chem. Soc., 98, 6747 (1976) have previously reported a trans orientated product from a thermal 'ene' reaction.

10. Yields were not optimised.

11. NMR Spectra were determined on a Perkin Elmer R12A (60 MHz) instrument except compound (3) where a Perkin Elmer R32 (90 MHz) was used. All samples contained T.M.S. as internal standard.

12. Prepared by vinyl magnesium bromide addition to heptaldehyde and subsequent oxidation.

13. Prepared by Reformatsky reaction of ethyl bromoacetate with octan-2-one, reduction and subsequent tosylation.

14. Preliminary data presented at the Fourth International Prostaglandin Conference (Washington, D.C., May 27, 1979).

The authors thank Mrs. D. Stoneham for her valuable technical assistance.

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(Received in UK 22 June 1979)