Tetrahedron Letters No. 17, pp 1525 - 1528.

0040-4039/79/0422-1525$02.00/0

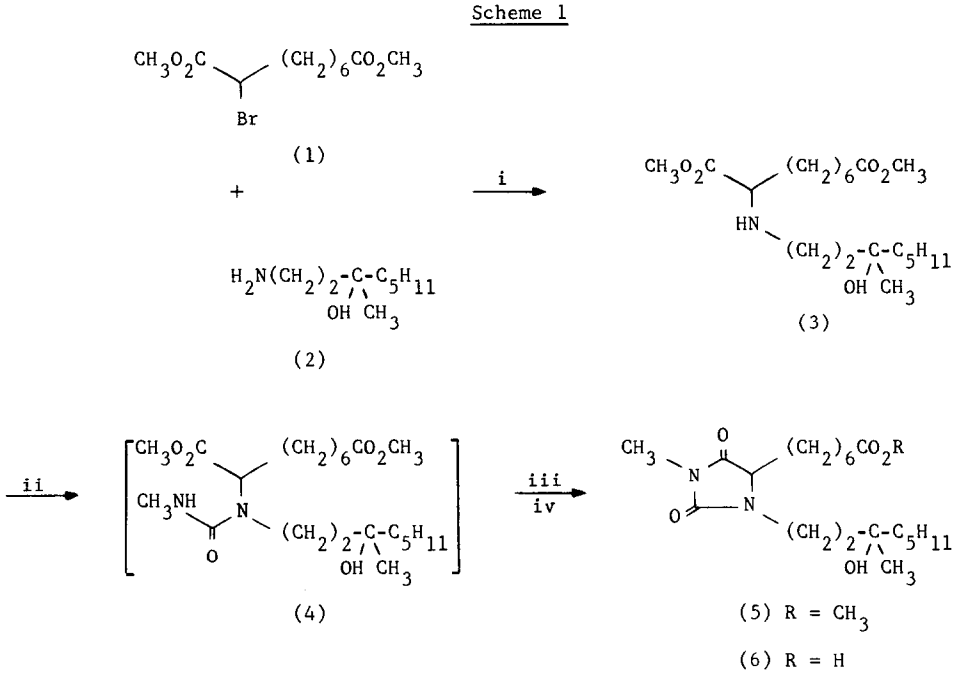
10,12-DIAZAPROSTAGLANDIN ANALOGUES

F. Cassidy and G. Wootton*

Beecham Pharmaceuticals, Medicinal Research Centre, The Pinnacles, Harlow, Essex, England.

Considerable interest has been shown recently in the synthesis and biological activities of azaprostaglandin analogues.[1-9] As a continuation of our work in this area,[3,9] we have developed a versatile, high yielding route (Scheme 1) to 10,12-diazaprostaglandin analogues from readily available starting materials.

Scheme 1



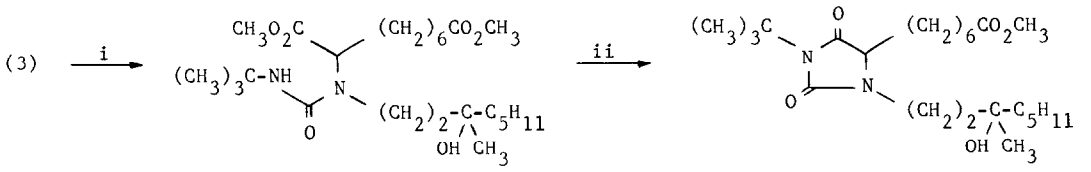
i; reflux in CH_3OH with Na_2CO_3

ii; CH_3NCO, toluene, room temperature

iii; reflux in toluene, 3 hr.

iv; K_2CO_3, H_2O, CH_3OH, reflux.

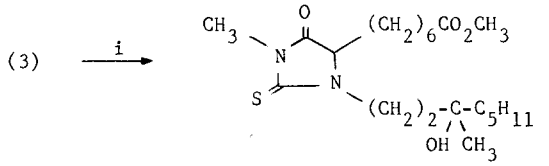
Methods for the synthesis of (1), (2) and (3) have been reported elsewhere.[3] Reaction of the amino di-ester (3) with methyl isocyanate gave, directly, the 10,12-diazaprostaglandin analogue (5), via thermal cyclisation of the intermediate urea derivative (4). The analogue (5), which was obtained as a colourless gum after column chromatography,[10] was subjected to alkaline hydrolysis to obtain the acid (6). The thermal cyclisation did not occur when tert-butylisocyanate was used in place of methyl isocyanate and the isolated product was the urea (7). However, the required 10,12-diazaprostaglandin analogue (8) was obtained, albeit in low yield, via cyclisation of (7) with potassium tert-butoxide in toluene. The yield of this cyclisation reaction was increased considerably when the diethyl rather than the dimethyl ester was used.



(7) (8)

i; $(CH_3)_3CNCO$, reflux in toluene, 3 hrs.
ii; $KOC(CH_3)_3$, reflux in toluene, 3 hrs.

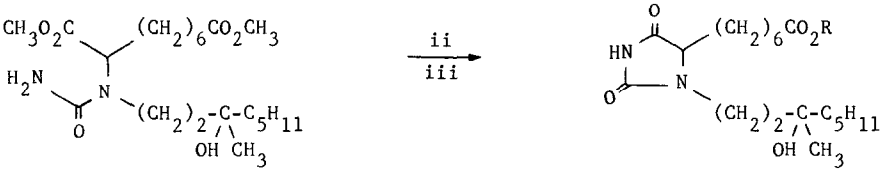
The route outlined in Scheme 1 was also used to produce a series of 11-thio-10,12-diaza-prostaglandin analogues. For example, reaction of the amino di-ester (3) with methyl isothiocyanate gave the ester (9) as a pale yellow gum after column chromatography.



(9)

i; CH_3NCS, reflux in toluene, 3 hrs.

In order to obtain 10-unsubstituted 10,12-diazaprostaglandin analogues, a different approach was necessary. For example, reaction of the amino di-ester (3) with potassium cyanate and dilute hydrochloric acid gave the urea (10) which was thermally cyclised to the 10,12-diazaprostaglandin analogue (11). Subsequent alkaline hydrolysis gave the acid (12).

(3) 

(10)

(11) R = CH_3

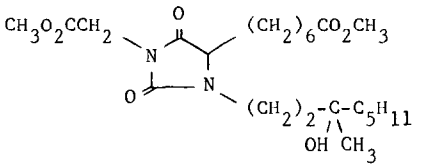
(12) R = H

i; 2N HCl, KCNO, 0°C, 0.5 hr.

ii; 100°C, 4 hr.

iii; K_2CO_3, H_2O, CH_3OH, reflux.

The acidic nature of the proton at the 10-position of (11) was utilised in an alternative route to the 10-substituted analogues. Thus, conversion of (11) to its 10-sodium salt, followed by treatment with methyl bromoacetate gave the di-ester (13) as a colourless gum after column chromatography.

(11) 

(13)

i; NaH, DMF, room temperature, 2 hrs.

ii; $CH_3O_2CCH_2Br$, DMF, room temperature, 5 hrs.

The 10,12-diazaprostaglandin analogues were obtained as mixtures of diastereoisomers.

Data for compounds (5) to (13)

Compound (5): Yield 82% from (3). IR: ν_{max}, (film), 3450, 1765, 1735, 1705 cm^{-1}. NMR[11]: τ, ($CDCl_3$), 7.75 (m, 2H, $C\underline{H}_2CO_2CH_3$); 7.25 (s, 1H, OH); 7.07 (s, 3H, NCH_3); 6.7 (brm, 2H, NCH_2); 6.38 (s, 3H, CO_2CH_3); 6.05 ppm (m, 1H, NCH). Mass spectrum: m/e (m*) requires 398.2778; found 398.2757.

Compound (6): Yield 86% from (5). IR: ν_{max}, (film), 3600 to 2400, 1760, 1700 (broad) cm^{-1} NMR: τ, ($CDCl_3$), 7.65 (t, 2H, $C\underline{H}_2CO_2H$); 7.0 (s, 3H, NCH_3); 6.6 (brm, 2H, NCH_2); 5.95 (t, 1H, NCH); 3.65 ppm (bs, 2H, CO_2H, OH). Mass spectrum: m/e (m*) requires 384.2622; found 384.2601.

Compound (7): Yield 85% from (3). IR: ν_{max}, (film), 3350, 1740, 1630 cm^{-1}. NMR: τ, (CCl_4), 7.75 (t, 2H, $C\underline{H}_2CO_2CH_3$); 7.1 (bs, 1H, OH); 6.8 (m, 2H, NCH_2); 6.4 (s, 3H, CO_2CH_3); 6.35 ppm (s, 3H, CO_2CH_3). Mass spectrum: m/e (m*) requires 472.3512; found 472.3511.

Compound (8): Yield 15% from (7). IR: ν_{max}, (film), 3450, 1760, 1740, 1700 cm^{-1}. NMR: τ, (CCl_4), 7.75 (t, 2H, $C\underline{H}_2CO_2CH_3$); 7.1 (s, 1H, OH); 6.8 (brm, 2H, NCH_2); 6.4 (s, 3H, CO_2CH_3); 6.25 ppm (m, 1H, NCH). Mass spectrum: m/e (m*) requires 440.3331; found 440.3258.

Compound (9): Yield 88% from (3). IR: ν_{max}, (film), 3470, 1740 cm^{-1}. NMR: τ, (CCl_4), 7.85 (t, 2H, $C\underline{H}_2CO_2CH_3$); 7.75 (s, 1H, OH); 6.7 (brm, 2H, NCH_2); 6.82 (s, 3H, NCH_3); 6.4 (s, 3H, CO_2CH_3); 5.9 ppm (brm, 1H, NCH). Mass spectrum: m/e (m*) requires 414.2549; found 414.2565.

Compound (10): Yield 100% (crude) from (3). IR: ν_{max}, (film), 3600 to 2800, 1720, 1660, 1600 cm^{-1}. NMR: τ, ($CDCl_3$), 7.75 (t, 2H, $C\underline{H}_2CO_2CH_3$); 6.8 (brm, 2H, NCH_2); 6.4 (s, 3H, CO_2CH_3); 5.95 ppm (m, 1H, NCH).

Compound (11): Quantitative yield from (10). IR: ν_{max}, (film), 3450, 3200, 1760, 1710 cm^{-1}. NMR: τ, (CCl_4), 7.75 (t, 2H, $C\underline{H}_2CO_2CH_3$); 6.7 (brm, 2H, NCH_2); 6.35 (s, 3H, CO_2CH_3); 5.95 ppm (m, 1H, NCH). Mass spectrum: m/e (m*) requires 384.2622; found 384.2620.

Compound (12): Quantitative yield from (11). IR: ν_{max}, (film), 3600 to 2500, 3400, 3200, 1760, 1710 cm^{-1}. NMR: τ, ($CDCl_3$), 7.65 (m, 2H, $C\underline{H}_2CO_2H$); 6.4 (brm, 2H, NCH_2); 5.9 (bs, 1H, NCH); 3.2 (bs, 2H, CO_2H, OH); 0.55 ppm (bs, 1H, CONHCO). Mass spectrum: m/e (m*) requires 370.2466; found 370.2473.

Compound (13): Yield 98% from (11). IR: ν_{max}, (film), 3450, 1760, 1720 (shoulder), 1710 cm^{-1} NMR: τ, (CCl_4), 7.75 (t, 2H, $C\underline{H}_2CO_2CH_3$); 7.15 (d, 1H, OH); 6.8 (brm, 2H, NCH_2); 6.4 (s, 3H, CO_2CH_3); 6.25 (s, 3H, CO_2CH_3); 5.95 (m, 1H, NCH); 5.85 ppm (s, 2H, $NC\underline{H}_2CO_2CH_3$). Mass spectrum: m/e (m*-H_2O) requires 438.2726; found 438.2719.

References, Notes and Acknowledgements

1. G. Bolliger and J.M. Muchowski, Tetrahedron Letters, 2931 (1975).
2. J.W. Bruin, H. deKonig and H.O. Huisman, Tetrahedron Letters, 4599 (1975).
3. Belgian Patent BE 835,989 (1976).
4. R.M. Scribner, Tetrahedron Letters, 3853 (1976).
5. P.A. Zoretic and F. Barcelos, Tetrahedron Letters, 529 (1977).
6. R.L. Smith, Ta-jyh Lee, N.P. Gould, E.J. Cragoe Jnr., H.G. Oien and F.A. Kuehl Jnr., J. Med. Chem., 20, 1292 (1977).
7. R.M. Scribner, Prostaglandins, 13, 677 (1977).
8. West German Patent DT 2724948 (1976).
9. West German Patent DT 2755771 (1976).

10. Column chromatography was carried out on silica gel using chloroform and/or chloroform methanol mixtures as eluants.
11. NMR spectra were determined on a Perkin Elmer R12A (60 MHz) instrument using TMS as internal standard.

The authors thank Miss K. Baker for valuable technical assistance.

(Received in UK 6 February 1979)