Syntheses of 9α,11α-Diacylamino-9,11-dideoxy-prostaglandin $F_{2\alpha}$ Analogues

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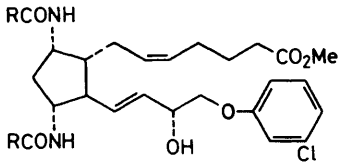
Summary The synthesis of the methyl esters of two 9α,11α-diacylamino-9,11-dideoxy-prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogues from an unstable 9α,11α-diazido-9,11-dideoxy-$PGF_{2\alpha}$ derivative in which triphenylphosphine is used to reduce the diazide to the diamine, is described.

NUMEROUS syntheses of prostaglandins in which one or more carbon atoms have been replaced by a nitrogen atom have been described.[1] However, the replacement of the 9- and 11-hydroxy-groups by the amino-group or its derivatives has received scant attention.[2] We report here the first synthesis of 9α,11α-diacylamino-9,11-dideoxy-prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) analogues, isolated as the methyl esters (**1a**) and (**1b**).†

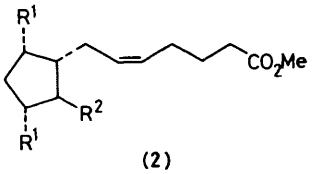
The readily available acetal[3] (**2a**) was chosen as a convenient starting material for the synthesis of compounds (**1a**) and (**1b**). Inversion of the two hydroxy-groups in the acetal (**2a**) was achieved in 40% overall yield‡ by reaction of compound (**2a**) with triphenylphosphine (3 equiv.), diethyl azodicarboxylate, and 4-phenylbenzoic acid[4] to give the 9β,11β-diester (**3a**), m.p. 115 °C, followed by hydrolysis of the diester (**3a**) with anhydrous K_2CO_3 in a dry MeOH–CH_2Cl_2 (2:1) mixture. Conversion of the diol (**3b**)§ into its dimesylate (**3c**) and then reaction of (**3c**) with sodium azide (8 equiv.) in aqueous dimethylformamide (100 °C, 3 h) gave the pyrroline (**4**) in 60% yield (p.t.l.c.§ developed with EtOAc) and none of the required diazide was formed. The pyrroline displayed a ν 1640 cm^{-1} band in its i.r. spectrum consistent with the 2-alkylpyrroline[5,6] rather than the alternative tetrahydropyridine structure.[7] However, when the dimesylate (**3c**) was treated with tetrabutylammonium azide in MeCN (25 °C, 72 h) a mixture of the unstable diazide (**2b**) and the cycloaddition product (**4**) was obtained. The diazide was readily separated by rapid silica column chromatography (eluted with Et_2O–CH_2Cl_2). Immediate reaction of the purified diazide with triphenylphosphine in MeCN (under argon) followed by hydrolysis of the intermediate phosphinimine (**2c**) with water gave the diamine (**2d**). Acetylation of the diamine with acetic anhydride produced, after p.t.l.c. (developed with acetone), the required diacetylamino-compound (**2e**) in 35% overall yield from the dimesylate (**3c**). The diamine was also acylated with benzoyl chloride to give, after p.t.l.c. [developed with EtOAC–CH_2Cl_2 (1:1)], the dibenzoylamino-derivative (**2f**) in 30% overall yield from the dimesylate (**3c**).

The acetal (**2e**) was transformed into the 15-keto-$PGF_{2\alpha}$ analogue (**5a**) in 40% overall yield by the following sequence of treatments. Toluene-*p*-sulphonic acid-catalysed hydro-



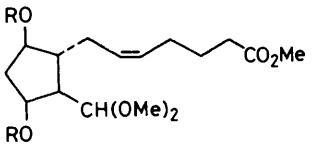
(1)

a; R = Me
b; R = Ph



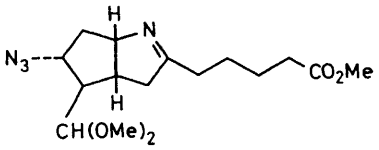
(2)

a; R^1 = OH, R^2 = $CH(OMe)_2$
b; R^1 = N_3, R^2 = $CH(OMe)_2$
c; R^1 = $N{=}PPh_3$, R^2 = $CH(OMe)_2$
d; R^1 = NH_2, R^2 = $CH(OMe)_2$
e; R^1 = NHCOMe, R^2 = $CH(OMe)_2$
f; R^1 = NHCOPh, R^2 = $CH(OMe)_2$
g; R^1 = NHCOMe, R^2 = CHO
h; R^1 = NHCOPh, R^2 = CHO

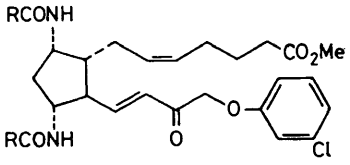


(3)

a; R = CO.C_6H_4.Ph—*p*
b; R = H
c; R = $MeSO_2$

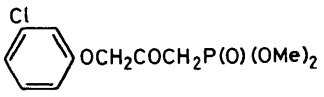


(4)



(5)

a; R = Me
b; R = Ph



(6)

† Work in this laboratory has shown that the luteolytic activity of $PGF_{2\alpha}$ is enhanced by replacement of the C(16)—C(20) fragment with an aryloxymethylene group (N. S. Crossley, *Prostaglandins*, 1975, **10**, 5).

‡ A mixture of olefins which resulted from the elimination at either the 9- or 11-position was isolated as a by-product. Similar observations have been noted by C. Gandolfi, A. Fumagalli, R. Pellegato, G. Doria, R. Ceserani, and J. Franceschini, *Farmaco, Ed. Sci.*, 1976, **31**, 649.

§ The structure assignments for the various intermediates in this communication were supported by i.r., n.m.r., and mass spectroscopy. Unless melting points are given, all the intermediates were oils and the yields quoted refer to materials obtained from column chromatography or, if specifically mentioned, preparative thin plate chromatography (p.t.l.c.) using Merck silica gel 60F 254 (2 mm) plates.

lysis of the acetal was followed by a Wittig-Horner [in a toluene–Bu^tOH (10:1) mixture with 1 N NaOH (1 equiv.) as base] reaction of the aldehyde (**2g**) with the phosphonate (**6**). Reduction of the resultant enone in CH_2Cl_2 with di-isobornyloxyaluminium isopropoxide[8] furnished, after p.t.l.c. (developed with acetone), a 60% yield of a mixture of compound (**1a**) and its 15β-epimer. The 15α-isomer¶ (**1a**), the major, less polar isomer, was separated from its epimer, after further p.t.l.c. [developed four times with CH_2Cl_2–Pr^iOH (3:1)] as an oil; δ ($CDCl_3$) 7·0 (m, 4 H, aromatic protons), 5·7 (m, 4 H, CH=CH), 4·5 (m, 1 H, CH–O), 3·9 (m, 2 H, O–CH_2), 3·65 (s, 3 H, MeO), 2·05 (s, 3 H, MeCONH), and 1·95 (s, 3 H, MeCONH); ν (CH_2Cl_2) 1730 (C=O) and 1670 cm^{-1} (C=O). The acetal (**2f**) was converted, by an analogous reaction sequence *via* the enone (**5b**), into a mixture of the required 15α-isomer (**1b**) and its 15β-epimer. The two isomers were separated using p.t.l.c. [developed with CH_2Cl_2–Me_2CO (4:1)] to give compound (**1b**), the major, less polar isomer, in 25% overall yield from the acetal (**2f**) as an oil; δ ($CDCl_3$) 8·05 (m, 2 H, aromatic protons), 7·7 (m, 2 H, aromatic protons), 7·1 (m, 10 H, aromatic protons), 5·5 (m, 4 H, CH=CH), 4·5 (m, 1 H, CH–O), 3·85 (m, 2 H, O–CH_2), and 3·6 (s, 3 H, MeO); ν (CH_2Cl_2) 1730 (C=O) and 1760 cm^{-1} (C=O).

In contrast with the high luteolytic activity shown by $PGF_{2\alpha}$ and its aryloxymethyl analogues,† the compounds (**1a**), (**1b**), and their 15β-epimers were inactive when assayed for luteolytic activity.

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¶ Structure assignments of the 15-epimers were based on observations, in this laboratory, that reduction of 9β,11β-diacylamino-9,11-dideoxy-$PGF_{2\alpha}$ 15-keto-derivatives and other $PGF_{2\alpha}$ 15-keto-analogues with di-isonorbornyloxyaluminium isopropoxide always gave the 15α-isomer as the major product.

[1] E. I. Leukoeva and L. J. Yakhontov, *Russ. Chem. Rev.* (*Engl. Transl.*), 1977, **46**, 565.
[2] G. L. Bundy and D. C. Peterson, *Tetrahedron Lett.*, 1978, 41.
[3] K. B. Mallion and E. R. H. Walker, *Synth. Commun.*, 1975, **5**, 221.
[4] A. K. Bose, B. Lal, W. A. Hoffmann, and M. S. Mankas, *Tetrahedron Lett.*, 1973, 1619.
[5] A. L. Logothetis, *J. Am. Chem. Soc.*, 1965, **87**, 749.
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[7] A. R. Katritzky and A. P. Ambler, 'Physical Methods in Heterocyclic Chemistry,' Vol. IV, Academic Press, New York, 1963, 186.
[8] J. Hutton, *Synth. Commun.*, 1979, **9**, 483.