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SYNTHESIS OF 10-AZAPROSTAGLANDINS

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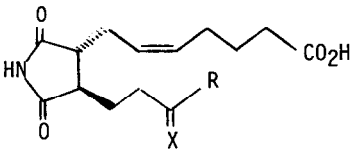
ABSTRACT : 10-Azaprostaglandin (succinimide) analogues (1a, b, c) were synthesised in a stereospecific manner from readily available materials.

In the search for therapeutically useful synthetic prostaglandins, heterocyclic analogues have received considerable attention.[1] This laboratory[2] and others[3] have recently reported the potent and diverse biological activities exhibited by the 10,12-diazaprostaglandins. Continuing our interest in this area we now describe the synthesis of 10-azaprostaglandin (succinimide) analogues (1a, b, c).[4]



1; a, R = C_5H_{11}, X = H_2
b, R = C_5H_{11}, X = H, OH
c, R = cyclohexyl, X = H, OH

Treatment of the sodio derivative of diethyl allyl malonate[5] with ethyl 2-bromo-decanoate afforded the expected triester (2a) which on hydrolysis and decarboxylation gave a mixture of *threo* (2b) and *erythro* (2c) acids.[5] Separation of the mixture by fractional crystallisation yielded the individual acids, and their homogeneity was confirmed by g.c. of their respective methyl esters. Both (2b) and (2c) on treatment with excess urea at 160° afforded the *trans*-succinimide (3a)[6] in good yield [g.c. 1 peak (OV 225), $\nu_{max.}$ 3230, 3080, 2930, 1780, 1715, 1642, 1180 cm^{-1}, δ 0.88 (3H, t, $CH_2\underline{CH_3}$),

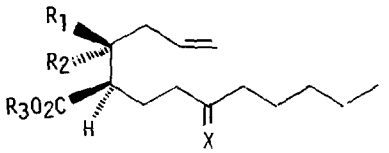
1.1 - 1.6 (14H, m), 2.4-2.7 (4H, m, $C\underline{H}_2.CH=CH_2$, 2 x $COC\underline{H}$), 4.9 - 6.0 (3H, m, $C\underline{H}$ = $C\underline{H}_2$), 9.35 (1H, br, $>N\underline{H}$)]. Ozonolysis of (3a) at -78° gave the aldehyde (4a) which was immediately subjected to a Wittig reaction ($Ph_3P=CH(CH_2)_3CO_2Na$, DMSO) yielding the azaprostaglandin (1a) as a colourless gum [Rf = 0.8 (SiO_2, $CHCl_3$-MeOH-AcOH, 18:1:1), $\nu_{max.}$ 3200, 1775, 1710, 1180 cm^{-1}, δ 0.88 (3H, t, $CH_2.C\underline{H}_3$), 1.0 - 2.6 (24H, m), 5.45 (2H, m, $C\underline{H}:C\underline{H}$), 9.5 (1H, br, $>N\underline{H}$), 10.08 (1H, br, $CO_2\underline{H}$), m/e 337 (M^+), $C_{19}H_{31}NO_4$ requires C, 67.65; H, 9.19; N, 4.15: Found C, 67.60; H, 9.28; N, 4.08].

A different approach was required in order to obtain the 15-hydroxy analogues. Oct-1-en-3-one (5a)[2] reacted smoothly with sodio diethyl malonate to give (6a) in good yield. The ketone function in (6a) was protected as the dithiolan (6b) (ethanedithiol, BF_3 etherate, 0°C) before reaction with ethyl 2-bromopent-4-enoate,[7] using sodium hydride in DMSO, to provide (2d) (50% yield). Saponification and decarboxylation of (2d) gave the anhydride (7) ($\nu_{max.}$ 2920, 2860, 1860, 1780, 1640 cm^{-1}), which on treatment with urea at 160° yielded the *trans*-imide (3b).[8] Column chromatography afforded (3b) as a white crystalline solid [m.p. 54-55°, R_f 0.66 (SiO_2, CH_2Cl_2-MeOH, 19:1), $\nu_{max.}$ 3220, 3078, 2920, 2860, 1775, 1705, 1640, 1180 cm^{-1}, δ 0.9 (3H, t, $CH_2C\underline{H}_3$), 1.25 - 2.1 (12H, m), 2.4 - 2.7 (4H, m, $C\underline{H}_2.CH=CH_2$, 2 x $COC\underline{H}$), 3.27 (4H, s, $-S.C\underline{H}_2.C\underline{H}_2S-$), 4.9 - 6.0 (3H, m, $C\underline{H}=C\underline{H}_2$), 9.25 (1H, br, $N\underline{H}$), m/e 341 (M^+), $C_{17}H_{27}NO_2S_2$ requires C, 59.82; H, 7.92; N, 4.10; S, 18.77: Found C, 60.00; H, 7.94; N, 3.98; S, 19.05]. Nuclear Overhauser and other double resonance data[8] confirmed the *trans*-geometry of (3b); the observed coupling constant of 4.8 Hz (J_{HA-HB}) was in agreement with the expected value (4-5 Hz). Treatment of (3b) with excess ceric ammonium nitrate in aqueous acetonitrile[9] regenerated the ketone function in (3c) [R_f 0.55 (SiO_2, $CHCl_3$-MeOH, 19:1, m/e 265 (M^+)] and this on reduction with sodium borohydride gave a mixture of epimeric alcohols (3d), distinguishable by t.l.c. [R_f 0.31 and 0.35 (SiO_2, $CHCl_3$-MeOH, 19:1) m/e 267 (M^+)]. Ozonolysis of (3d) provided the aldehyde (4d) which underwent a Wittig reaction with $Ph_3P=CH.(CH_2)_3CO_2Na$ in dimethyl sulphoxide to yield the desired azaprostaglandin (1b) as an epimeric mixture, also distinguishable by t.l.c. [R_f 0.48 and 0.54 (SiO_2, $CHCl_3$-MeOH-AcOH, 18:1:1)]. The oily mixture (1c) gave[$\nu_{max.}$ 3200, 2930, 2860, 1770, 1710, 1180 cm^{-1}, δ 0.87 (3H, t, $CH_2.C\underline{H}_3$), 1.0 - 2.1 (16H, m), 2.3 (2H, t, $C\underline{H}_2.CO_2H$), 2.4 - 2.7 (4H, m, $>CH.C\underline{H}_2CH=CH_2$-, 2 x $COC\underline{H}$), 3.53 (1H, m, $C\underline{H}OH$), 5.46 (2H, m, $C\underline{H}=C\underline{H}$), δ (2H, br, $O\underline{H}$ and $CO_2\underline{H}$), 9.5 (1H, br, $>N\underline{H}$), found m/e 353.2199 (M^+; $C_{19}H_{31}NO_5$ requires m/e 353.2197)].

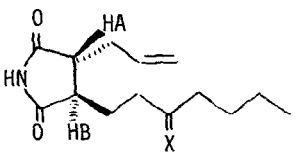
The methods already described were also used to synthesise various analogues of (1b) from the readily available vinyl ketones (5, R = alkyl, cycloalkyl etc.).[2] For example, the cyclohexyl analogue (1c) [10] was obtained as an epimeric mixture from cyclohexylprop-1-en-3-one (5b), *via* the imide (8) [m.p. 74-76°, m/e 353 (M^+)], in the manner described for (1b).

Separation of the mixtures (1b) and (1c) by h.p.l.c. afforded the individual epimers.

The less polar epimers of (1b) and (1c) had 1/10th of the potency of PGE_1 as inhibitors of platelet aggregation in human platelet-rich plasma.



2; a, $R_1 = R_2 = EtO_2C$, $R_3 = Et$, $X = H_2$
b, $R_1 = H$, $R_2 = HO_2C$, $R_3 = H$, $X = H_2$
c, $R_1 = HO_2C$, $R_2 = H$, $R_3 = H$, $X = H_2$
d, $R_1 = R_2 = EtO_2C$, $R_3 = Et$, $X = -S.CH_2CH_2S-$



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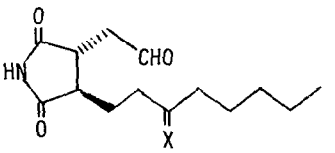

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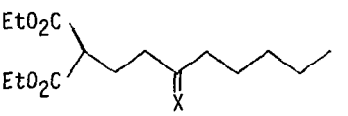
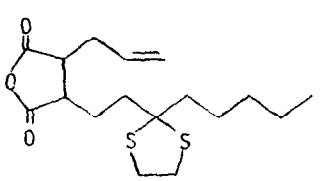
a, X = H_2
b, X = $-S.CH_2.CH_2.S-$
c, X = O
d, X = H, OH

$CH_2=CH.COR$



5; a, R = C_5H_{11}
R = cyclohexyl

6; a, X = O
b, X = $-S.CH_2.CH_2.S-$



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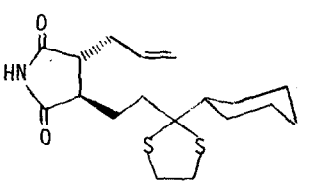

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References and Notes

1 (a) R. M. Scribner, *Tetrahedron Letts.*, 3853 (1976) (b) P. A. Zoretic and F. Barcelos, *ibid*, 529 (1977) (c) G. Bolliger and J. M. Muchowski, *ibid*, 2931 (1975) (d) D. Reuschling, M. Mitzloff, K. Kuhlein, *ibid*, 4467 (1976) (e) E. I. Levkoeva and L. N. Yakhontov, *Russ. Chem. Rev.*, 46, 565, 1977.

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4 The compounds described in this paper were synthesised as racemic compounds; the structural formulae 1-4 and 8 depict their relative configuration.

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6 Heating *cis*-succinimides in the presence of urea at 160° affords the thermodynamically more stable *trans*-isomers. J. H. Golden and R. P. Linstead, *J. Chem. Soc.*, 1958, 1732.

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8 Studies with Lanthanide shift reagents in conjunction with homonuclear decoupling confirmed the assignment of the methine proton H_A and allowed a measurement of J_{AB}= 4.8 Hz. For a pair of isomers, J_{AB} (cis) is greater than J_{AB} (trans) in planar five-membered rings, and confirmation of a *trans* configuration in (3b) was obtained by comparing the above value with the coupling in succinimide itself. Computer analysis of the satellite lines arising from natural abundance ^{13}C in succinimide, of which the 'H spectrum consists of the AA'BB' part of an AA'BB'X system, gave a value of J_{AB} (trans) = 4.4 Hz.

9 T. L. Ho, H. C. Ho and C. M. Wong, *J.C.S. Chem. Commun.*, 791, (1972).

10 1c [$\nu_{max.}$ 3250, 2925, 2860, 1772, 1710, 1178 cm^{-1}, δ 0.98 - 2.0 (19H, m), 2.3 (2H, t, $C\underline{H}_2.CO_2H$), 2.4 - 2.7 (4H, m, $CH.C\underline{H}_2$-CH:CH_2, 2 x $COC\underline{H}$), 3.5 (1H, m, $C\underline{H}OH$), 5.2 (2H, br, $O\underline{H}$ and $CO_2\underline{H}$), 5.45 (2H, m, $C\underline{H}$=$C\underline{H}$), 9.2 (1H, br, $N\underline{H}$), found $^m/e$ 365.2192 (M^+; $C_{20}H_{31}NO_5$ requires $^m/e$ 365.2192)].

11 I should like to thank Mr. A. Ferrige, Drs. J. Lindon and F. Cottee and their colleagues for the spectroscopic data, Mr. P. Baker for the analytical data, Dr. S. Moncada and his colleagues for the biological data, Mr. D. Demaine for valuable technical assistance and finally Drs. H. Hodson and N. Whittaker for helpful discussion.

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