SYNTHESIS OF 9-AZAPROSTAGLANDIN ANALOGS

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9,11-Dideoxy-9-aza-prostaglandin derivatives are synthesized in nine steps starting from diethyl 7-cyano-heptylidenemalonate.

The interest in novel prostaglandins with specific pharmacological properties has recently led to the synthesis of prostaglandin analogs in which carbon atoms of the 5-membered ring are replaced by hetero atoms. Syntheses of 9-oxa (2), 10-oxa (3), 11-oxa (4), 9,11-dioxa (5), 9-thia (6), 11-thia (7), 8-aza (8) and 8,12-diazaprostaglandins (9) have been described. We now want to report the synthesis of another class of heterocyclic analogs, the 9,11-dideoxy-9-aza-prostaglandin derivatives 8b,c and 9b,c (10).

The crude product from the Michael addition of aziridine (11) to diethyl 7-cyanoheptylidenemalonate 1a (12), was treated with ethyl chloroformate to give urethane 2a [IR 2220, 1720, 1685 cm^{-1}; NMR ($CDCl_3$) δ 3.5 (m, Cl-CH_2-CH_2-N-), 2.3 (t, J=7 Hz, -CH_2CN)] which was purified by column chromatography over silica gel. Ring closure of 2a by reaction with sodium hydride in benzene at room temperature provided pyrrolidine derivative 3a [IR 2220, 1720, 1690; NMR ($CDCl_3$) 4.6 (br t, J=6.5 Hz, N-CH-R), 3.4 (dd, J=4 Hz and 9.5 Hz, N-CH_2-), 2.35 (t, J=7 Hz, -CH_2CN)] in 80% yield from 1a after purification over silica gel.

Decarbethoxylation of 3a [dimethyl sulfoxide, water, sodium chlo-

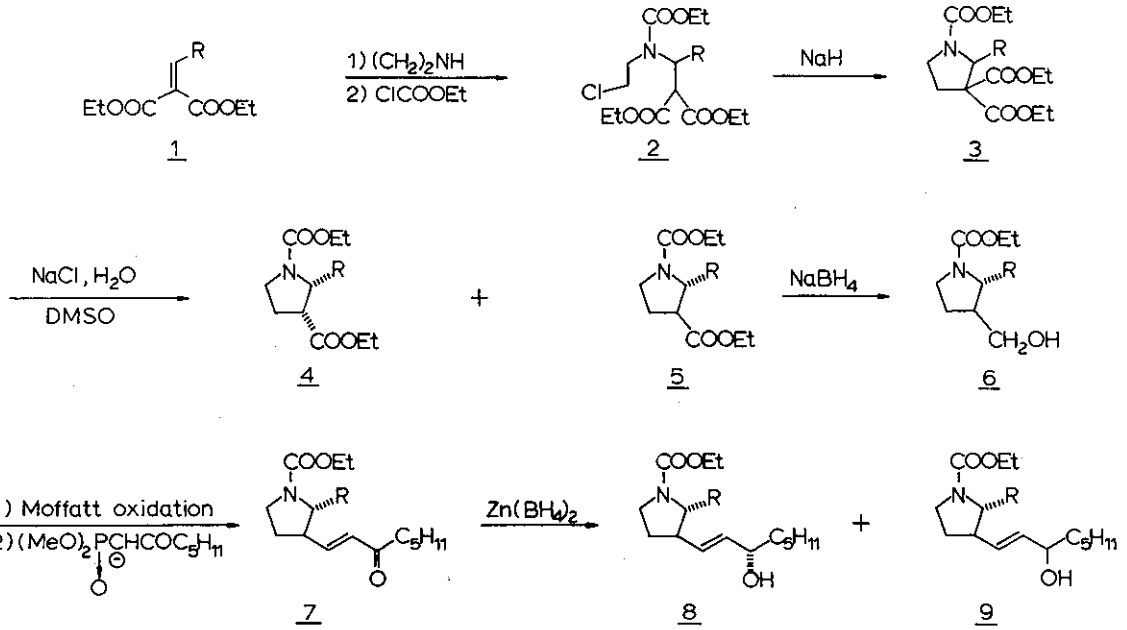
ride; 175° (13)] led to the formation of a mixture of cis-trans isomers 4a and 5a (66%; 1:5) which on epimerization (potassium carbonate, ethanol; reflux) afforded mainly trans isomer 5a [IR 2220, 1720, 1690; NMR ($CDCl_3$) 2.10 (m, N-CH_2-CH_2-), 2.32 (t, J=7 Hz, -CH_2CN), 2.76 (m, $J_{2,3}$=3 Hz, >CHCOOEt)].

Reduction of 5a with sodium borohydride in ethanol at room temperature gave the alcohol 6a [90%; IR 3450, 2230, 1690; NMR ($CDCl_3$) 2.10 (m, N-CH_2-CH_2-), 2.32 (t, J=7 Hz, -CH_2CN), 3.46 (d, J=7 Hz, -CH_2OH)]. Hydrolysis of the nitrile group in 6a (potassium hydroxide, methanol, water; 110°) followed by esterification of the resulting carboxylic acid with diazomethane gave the methyl ester 6b [70%; IR 3450, 1725, 1690; NMR ($CDCl_3$) 2.0 (m, N-CH_2-CH_2-), 2.28 (t, J=7 Hz, -CH_2COOMe), 3.0 (br, exchangeable in D_2O), 3.46 (d, J=7 Hz, -CH_2OH), 3.63 (s, -COOCH_3)].

The alcohol function in 6b was oxidized [dimethyl sulfoxide, dicyclohexylcarbodiimide, trifluoroacetic acid, pyridine, benzene (14)] to the corresponding aldehyde which - without foregoing purification - was converted [dimethyl 2-oxoheptylphosphonate, sodium hydride, tetrahydrofuran (15)] to the enone 7b [45%; IR 1725, 1690, 1620; NMR ($CDCl_3$) 0.9 (t, J=6.5 Hz, CH_2-CH_3), 2.31 (t, J=7 Hz, -CH_2COOMe), 2.54 (t, J=7 Hz, -COCH_2-), 2.75 (m, >CH-C=C), 6.14 (d, $J_{13,14}$=16 Hz, CH=CH-CO), 6.74 (q, $J_{12,13}$=8 Hz, $J_{13,14}$=16 Hz, CH=CH-CO)]. Reduction of the C_{15}-carbonyl function in 7b (zinc borohydride, dimethoxy ethane; room temperature) produced a mixture of the C_{15}-epimeric alcohols 8b and 9b [70%; IR 3450, 1720, 1680; NMR ($CDCl_3$) 0.9 (t, J=6.5 Hz, CH_2CH_3), 2.31 (t, J=7 Hz, -CH_2COOMe), 2.56 (m, >CH-CH=CH), 3.65 (s, COOCH_3), 5.57 (m, -CH=CH-)], which could be separated by chromatography over silica gel (ethyl acetate/cyclohexane 1:1).

Reactions analogous to those described above converted tri-ester 1c (16) into 5c. Regioselective reduction (sodium borohydride, ethanol; room temperature) of the C_{12}-ester function (17) furnished alcohol 6c

[55%; IR 3450, 1725, 1690; NMR ($CDCl_3$) 2.29 (t, J=7 Hz, $C\underline{H}_2COOEt$), 3.46 (d, J=7 Hz, $-C\underline{H}_2OH$)], which was converted - via the enone 7c - to the mixture of C_{15} - alcohols 8c and 9c (spectra very similar to 8b and 9b).



a R = $(CH_2)_6CN$
b R = $(CH_2)_6COOMe$
c R = $(CH_2)_6COOEt$

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