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-cyanoheptylidemalonate.

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 \( \text{8b}, \text{c} \) and \( \text{9b}, \text{c} \) (10).

The crude product from the Michael addition of aziridine (11) to diethyl 7-cyanoheptylidemalonate \( \text{1a} \) (12), was treated with ethyl chloroformate to give urethane \( \text{2a} \) [IR 2220, 1720, 1685 cm\(^{-1}\); NMR (CDCl\(_3\)) \( \delta \) 3.5 (m, Cl-CH\(_2\)-CH\(_2\)-N-), 2.3 (t, J=7 Hz, -CH\(_2\)CN)] which was purified by column chromatography over silica gel. Ring closure of \( \text{2a} \) by reaction with sodium hydride in benzene at room temperature provided pyrrolidine derivative \( \text{3a} \) [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\(_2\)CN)] in 80\% yield from \( \text{1a} \) after purification over silica gel.

Decarbethoxylation of \( \text{3a} \) [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 (CDCl₃) 2.10 (m, N-CH₂-CH₂-), 2.32 (t, J=7 Hz, -CH₂CN), 2.76 (m, J₂,₃=3 Hz, -CH₂COEt)]. Reduction of 5a with sodium borohydride in ethanol at room temperature gave the alcohol 6a [90%; IR 3450, 2230, 1690; NMR (CDCl₃) 2.10 (m, N-CH₂-CH₂-), 2.32 (t, J=7 Hz, -CH₂CN), 3.46 (d, J=7 Hz, -CH₂OH)]. 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 (CDCl₃) 2.0 (m, N-CH₂-CH₂-), 2.28 (t, J=7 Hz, -CH₂COOMe), 3.0 (br, exchangeable in D₂O), 3.46 (d, J=7 Hz, -CH₂OH), 3.63 (s, -COOCH₃)].

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 (CDCl₃) 0.9 (t, J=6.5 Hz, CH₂CH₃), 2.31 (t, J=7 Hz, -CH₂COOMe), 2.54 (t, J=7 Hz, -COCH₂-), 2.75 (m, CH-C≡C), 6.14 (d, J₁₃,₁₄=16 Hz, CH=CH-CO), 6.74 (q, J₁₂,₁₃=8 Hz, J₁₃,₁₄=16 Hz, CH=CH-CO)]. Reduction of the C₁₅-carbonyl function in 7b (zinc borohydride, dimethoxy ethane; room temperature) produced a mixture of the C₁₅-epimeric alcohols 9b and 9b [70%; IR 3450, 1720, 1680; NMR (CDCl₃) 0.9 (t, J=6.5 Hz, CH₂CH₃), 2.31 (t, J=7 Hz, -CH₂COOMe), 2.56 (m, CH=CH-C≡C), 3.65 (s, COOCH₃), 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 C₁₂-ester function (17) furnished alcohol 6c
HETEROCYCLES, Vol. 4, No. 4, 1976

[55%; IR 3450, 1725, 1690; NMR (CDCl₃) 2.29 (t, J=7 Hz, CH₂COOEt), 3.46 (d, J=7 Hz, -CH₂OH)], which was converted - via the enone 7c - to the mixture of C₁₅ - alcohols 8c and 9c (spectra very similar to 8b and 9b).

\[ R \]  
\[ \text{EtOOC} \quad \text{COOEt} \]  
\[ 1 \]  
\[ \text{1)} (\text{CH₂})₂\text{NH} \quad \text{2)} \text{ClCOOEt} \]  
\[ \text{EtOOC} \quad \text{COOEt} \]  
\[ 2 \]  
\[ \text{NaH} \]  
\[ \text{COOEt} \quad \text{COOEt} \]  
\[ 3 \]  
\[ \text{NaCl, H₂O \quad DMSO} \]  
\[ \text{COOEt} \]  
\[ 4 \]  
\[ + \]  
\[ \text{COOEt} \]  
\[ 5 \]  
\[ \text{NaBH₄} \]  
\[ \text{COOEt} \]  
\[ 6 \]  
\[ 1) \text{Moffatt oxidation} \quad 2) (\text{MeO})₂\text{POCHCOCH}_₃ \]  
\[ \text{COOEt} \]  
\[ 7 \]  
\[ \text{Zn(BH₄)_2} \]  
\[ \text{COOEt} \]  
\[ 8 \]  
\[ \text{COOEt} \]  
\[ 9 \]  
\[ a \ R = (\text{CH}₂)₆\text{CN} \]  
\[ b \ R = (\text{CH}₂)₆\text{COOMe} \]  
\[ c \ R = (\text{CH}₂)₆\text{COOEt} \]
REFERENCES

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4. I.T. Harrison, V.R. Fletcher, and J.H. Fried, ibid., 1974, 2733;
10. The synthesis of a 9-deoxy-9-aza analog will be published elsewhere.
16. Obtained from ethyl 7-formylheptanoate by the method given in reference 12.
17. Prostaglandin numbering.

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