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SYNTHETIC STUDIES ON PROSTAGLANDINS II*

A NOVEL SYNTHESIS OF METHYL ESTERS OF 15-DEHYDRO-PGB$_1$ AND PGE 237

Masateru Miyano

G. D. Searle & Co., Skokie, Illinois 60076, U.S.A.

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The previously undisclosed stereochemistry of bicyclo[2.2.1]hept-5-ene-3-n-hexanoyl-2-carboxylic acid(1,2) and related derivatives was determined by nmr analysis(3) and application of Fraser's rule(4,5). It was concluded that the compound in question is the 3-exo-n-hexanoyl-2-endo-carboxylic acid(I). This conclusion was supported by chemical evidence, that is, I gave rise to the iodolactone II(6): ir($CHCl_3$) 5.58(lactone), 5.81(ketone), in good yield using the standard iodolactonization procedure(7).

I was converted into the chloroketone(III) by successive treatment with oxalyl chloride, excess diazomethane, and hydrogen chloride. The low melting III boiling at 146-7°(0.2 mm): ir($CHCl_3$) 5.76($COCH_2Cl$), 5.83(ketone); nmr($CDCl_3$) τ 5.84(s, 2, $COCH_2Cl$), 6.29(t, 1, J = 4 Hz, C-2-exo H), was further characterized as the pyridinium chloride(IV)(6), mp 186° and the nitrone(V), mp 125°(6).

The condensation product(VI) of III and the sodium enolate of dimethyl 3-ketoundecanoate(8) was cyclized with alkali. The subsequent decarboxylation in quinoline followed by esterification with diazomethane afforded VII, which underwent pyrolysis at 165-180° giving VIII(methyl ester of 15-dehydr [illegible]GB$_1$)(6): uv(MeOH) 296 mμ(ε 22,800); nmr($CDCl_3$) τ 2.35(d, 1, J = 15.5 Hz, C-13 [illegible].45(d, 1, J = 15.5 Hz, C-14 H). Assuming that the C-13 and C-14 substitu[illegible]

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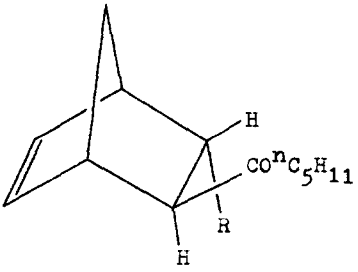
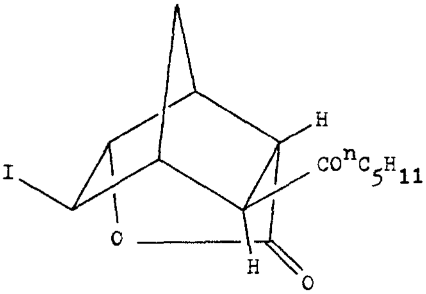
* Part I : M. Miyano and C. R. Dorn, Tetrahedron Letters, in press.

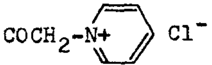


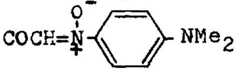


II

I R = CO_2H

III R = $COCH_2Cl$

IV R = 

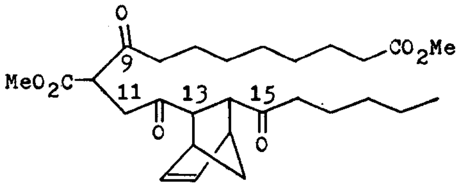
V R = 

VII are endo and exo respectively, the predicted geometry of the 13,14-double bond in VIII would be trans based upon the principle of the conservation of orbital symmetry(9) and was actually found to be trans as demonstrated by the coupling constant of the olefinic protons(see above). The calculated uv maximum for VIII is 298 mμ(10) which is in good agreement with the synthetic compound.

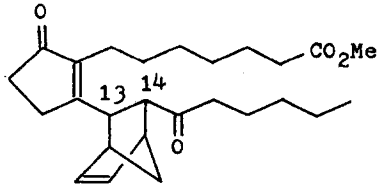
The bicyclo system functions as an excellent protecting group, since only one mode of condensation(VI ⟶ VII) occurs, although VI contains three ketonic groups and three reactive methylenes in addition to three reactive methines. More specifically, the rigid system in VI holds the C-13-endo and the C-14-exo substituents far enough apart to prohibit undesirable condensations(for example, between C-11 and C-15). The bicyclo system makes the C-13 and -14 carbons tertiary ones, thus preventing undesirable condensations, for example, between C-9 and C-14(no dehydration can take place).

VIII was futher characterized as the oxime(IX)(6): mp 120.5°; uv(MeOH) 308 mμ(ε 38,400), 317 mμ(ε 38,300); nmr(warm $CDCl_3$) τ 2.99(d, 1, J = 16 Hz), 3.63(d, 1, J = 16 Hz), 6.34(s, 3), 7.28(broad s, 4, C-9 and C-10 protons).

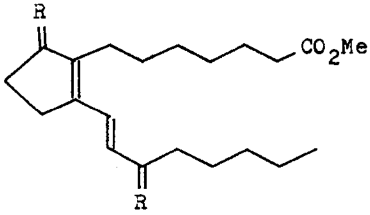
Änggård treated 15-dehydro-PGE_1(X) with 0.5 N sodium hydroxide giving rise to a new compound(uv in ethanol 280 mμ) to which the structure VIII was incorrectly assigned(11). Compound XI(uv in methanol 282 mμ) was obtained as a byproduct in our total synthesis of X(12) and is probably identical with Änggård's compound(3). The methyl ester(XII) was totally synthesized by Morin



VI

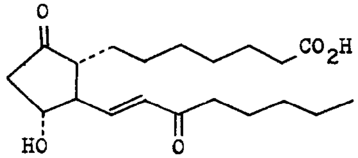


VII

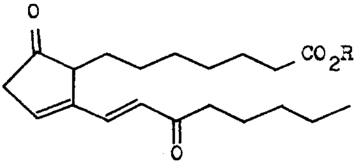


VIII R = O

IX R = NOH

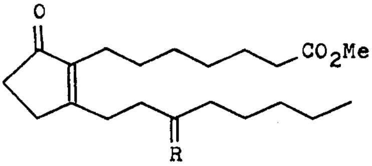


X



XI R = H

XII R = Me



XIII R = O

XIV R = H, OH

(13) and the identity of the chromophore with Änggård's compound was suggested.

Reduction of VIII with zinc powder in acetic acid afforded XIII(6): ir (CHCl$_3$) 5.76-5.87(carbonyls), 6.09(C=C); uv(MeOH) 238 mμ(ε 13,400); nmr(CDCl$_3$) τ 7.32(s, 4, C-13 and C-14 protons). Hydrogenation of VIII over palladium on carbon gave rise to approximately equal amounts of XIII and XIV(methyl ester of PGE 237)(6). The synthetic XIV was indistinguishable from the authentic optically active XIV(14) in their ir and uv spectra.

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