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SYNTHESIS OF BENZO-TYPE PROSTAGLANDIN ANALOGS[1)]

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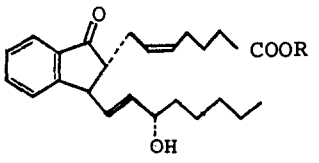
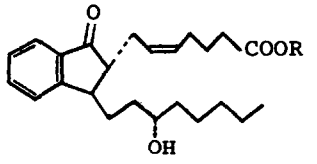
In recent years, a number of modified prostaglandins(PG) have been synthesized at several laboratories from synthetic and pharmaceutical points of view.[2)]

As part of our program of structural modification on PG, attempts have been made to synthesize benzo-type PG derivatives, a new class of PG analogs.

We wish to describe here the synthesis of 10,11-benzo-PGA_2 1 and its 13,14-dihydro derivative 2.





1 R= H, 17 R= CH_3 2 R= H, 21 R= CH_3

Alkylation of indenyllithium with chloromethyl methylether gave 1-methoxymethyl-indene(3, b.p. 50°/0.2 mm) in 78% yield[3)], which was lactonized with manganic triacetate[4)] in acetic acid and acetic anhydride at reflux for 0.5 hr to give the indan lactone[5)] (4, in 68% yield; ν_{max} 1775; m/e 218(M^+)).

The lactone 4 was reduced with diisobutylaluminium hydride in toluene at -60°, and the resulting hemiacetal was condensed with disodium salt of 5-triphenylphosphoniopentanoic acid in dimethyl sulfoxide at room temperature to yield the indanyl hexenoic acid 5, which was converted to the methyl ester 6.

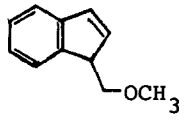
Direct demethylation of 6 or its acetate 7 to 12 or 11 failed since undesired dehydration or ring expansion occurred yielding a complex mixture of indene or dihydronaphtalene products.

Therefore demethylation with boron tribromide was carried out on indanone ester 8(ν_{max} 1735,1710,1605; m/e 316(M^+)), which was obtained from 6 by oxidation with active manganese dioxide, to obtain the hydroxymethyl indanone 9.

The tetrahydropyranyl ether of 9 was reduced with sodium borohydride to yield 10. Acetylation of 10, followed by hydrolysis with aq. acetic acid and tetrahydrofuran afforded the desired hydroxymethyl indanol acetate 11(in 68% yield from 8; ν_{max} 3400,1735). Oxidation of 11 with Collins reagent in methylene chloride at 0° yielded the aldehyde 13, which was condensed with the sodio derivative of dimethyl 2-oxo-heptyl phosphonate in tetrahydrofuran at room temperature to afford the enone 14(in 54% yield from 11; ν_{max} 1740,1695,1630; m/e 440(M^+), 380(M^+-60)). Reduction of 14 with sodium borohydride yielded the alcohol 15, which was successively subjected to tetrahydropyranylation and deacetylation by usual procedures to afford 16. Oxidation of 16 with Collins reagent followed by hydrolysis yielded 10,11-benzo-PGA_2 methyl ester 17(in 78% yield from 14; ν_{max} 3400,1740,1715,1605; nmr. δ 5.70(2H, m), 5.43(2H, m)). Saponification of 17 with pottasium carbonate in aq. methanol afforded the objective 10,11-benzo-PGA_2 1[6] (ν_{max} 3400,2650,1710,1605).

On the other hand, 13,14-dihydro-10,11-benzo-PGA_2 2 was obtained by the similar procedures described above. The Grignard reaction of 1-(2'-bromoethyl)-indene (b.p. 97°/0.1mm, prepared from indenyllithium and 1,2-dibromoethane) with n-hexanal in ether produced 1-(3'-hydroxyoctyl)-indene 18 in 57% yield. Treatment of 18 with manganic triacetate to afford the acetoxylactone 19(in 52% yield; ν_{max} 1780,1735). The lactone 19 was reduced with diisobutylaluminium hydride to the hydroxy-hemiacetal,. which was condensed with disodium salt of 5-triphenylphosphoniopentanoic acid to afford the acid 20. The methyl ester of 20 was oxidized with active manganese dioxide to afford the indanone 21(in 40% yield from 19; ν_{max} 3400,1735,1605; nmr. δ 5.37(2H, m); m/e 400(M^+),382(M^+-18)), which was saponified with aq. methanol to afford the objective 13,14-dihydro-10,11-benzo-PGA_2 2[6] (ν_{max} 3400,2650,1710,1605).

The compounds(1, 2) showed some significant PG like activities such as gastric acid antisecretion or hypotensive activity.



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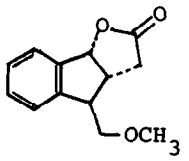

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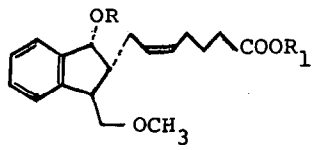
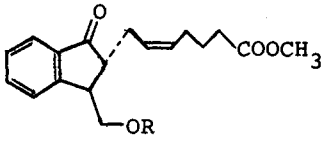


5 R= H, R_1= H

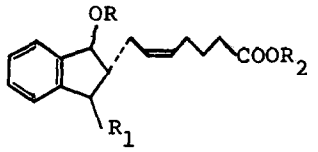
6 R= H, R_1= CH_3

7 R= $COCH_3$, R_1= CH_3



8 R= CH_3

9 R= H



10 R= H, R_1= CH_2OTHP, R_2= CH_3

11 R= $COCH_3$, R_1= CH_2OH, R_2= CH_3

12 R= H, R_1= CH_2OH, R_2= CH_3

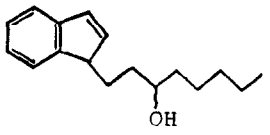
13 R= $COCH_3$, R_1= CHO, R_2= CH_3

14 R= $COCH_3$, R_1= $CH{=}CHCO(CH_2)_4CH_3$, R_2= CH_3

15 R= $COCH_3$, R_1= $CH{=}CHCH(OH)(CH_2)_4CH_3$, R_2= CH_3

16 R= H, R_1= $CH{=}CHCH(OTHP)(CH_2)_4CH_3$, R_2= CH_3

20 R= H, R_1= $CH_2CH_2CH(OH)(CH_2)_4CH_3$, R_2= H



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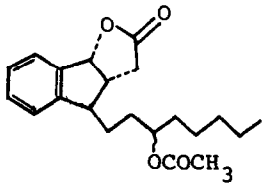

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References and notes

1) Synthetic studies on cyclopentane derivatives Part VIII; proceeding paper of this series. : H. Shimomura, A. Sugie, J. Katsube and H. Yamamoto, Tetrahedron Letters, 4099(1976).

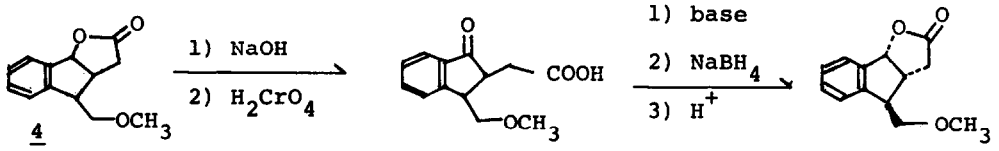
2) For examples; P. Crabbe, H. Carpio and A. Guzman, Intra. Sci. Chem. Rep., 6, 55(1972); P. Crabbe, Chem. in Britain, 11, 132(1975).

3) No amount of the double bond migrated isomer was detected by nmr in this reaction. See; L. Cedheim and L. Eberson, Synthesis, 159(1973); L. Meuring, Acta. Chem. Scand., 28, 295(1974).

4) J.B. Bush and H. Finkbeiner, J. Am. Chem. Soc., 90, 5903(1968); E.J. Heiba, R.M. Dessau and W.J. Koehl, ibid., 90, 5905(1968).

5) The relative configuration between the lactone moiety and the methoxymethyl group is assigned to be trans by following examinations;

A. The same lactone was obtained from 4 in following reactions.



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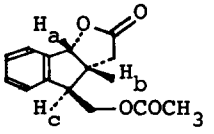
B. The vicinal coupling constants observed by spin-decoupling experiments are consistent with the assigned stereochemistry.



J_{ab} = 5 cps

J_{bc} = 1 cps

6) This product was composed of a mixture of the desired 15-α-OH compound and its 15-epimer(prostanoid numbering), which was subjected to the biological examination without separation. The ratio was found to be almost 1:1 on T.L.C.(Benzene:AcOEt:AcOH = 20:2:1 by 3 times developments); 0.30:0.28 for 1 and its epimer; 0.29:0.27 for 2 and its epimer.