THE SYNTHESIS OF NEW DERIVATIVES AND HOMOLOGUES OF PROSTANOIC ACID*

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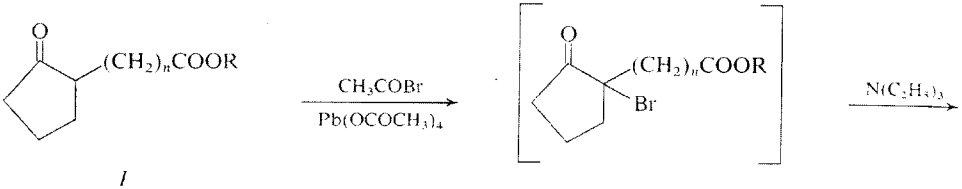
A new route for the preparation of esters of ω-(2-oxo-5-cyclopentyl)alkanoic acids *II* has been elaborated. Corresponding esters of ω-[5-(1-hydroxyalkyl)-2-oxocyclopentyl]-alkanoic acids *III* have been prepared on radical addition to esters *II*.

On the basis of the knowledge concerning the physiological effect of prostaglandin analogues and substances with the simplified structure of prostanoic acid experiments were carried out aiming at the elaboration of a new route for the preparation of homologues of prostanoic acid derivatives having a hydroxyl group in the position 13. For this purpose the radical addition of primary alcohols to α,β-unsaturated ketones *II* has been employed. We succeeded in isolating the corresponding esters of homo- or nor-9-oxo-13-hydroxyprostanoic acids the possible physiological activity of which will be published elsewhere. The preparation of unsaturated acid *IIc* (R = H) has already been described in literature[1,2], and it has been used[3] for the synthesis of racemic prostaglandin B_1. Ethyl ester *IId* has also been mentioned in literature[4], which was also used for the synthesis of the last mentioned substance, but neither its physical constants nor the method of its preparation have been described.

Using the new bromination reagent, *i.e.* a solution of acetyl bromide and lead tetraacetate in dichloromethane, ester of the ω-(2-oxocyclopentyl)alkanoic acid[5] *I* was converted to corresponding 1-bromo derivatives which were reacted without isolation with tertiary amine to give the ester of ω-(2-oxo-5-cyclopentenyl)alkanoic acid *II*. In the reaction of the reagent used a mechanism is supposed which has already been described in a similar reaction with acetyl chloride[6]. The by-product, an ester of ω-(1-acetyl-2-oxocyclopentyl)alkanoic acid, which may be expected according to the mechanism proposed, was not isolated. Dehydrobromination was carried out by boiling the crude bromoester with triethylamine or with dimethylaniline in ether or in benzene. Pure bromo derivative could not be isolated, because it splits off hydrogen bromide easily, especially on distillation, so that unsaturated ketoester *II* can be also prepared by repeated distillation of crude bromo derivative under

* This paper is a continuation of the study in ref.[5].

reduced pressure. The prepared homologues *II* were characterized by infrared spectra in which a maximum occurred characteristic of conjugated double bond (1630 to 1640 cm^{-1}) and two different maxima for carbonyl functions. In the case of derivative *IIc* its ^{1}H-NMR spectrum was measured, which was analogous with the described ^{1}H-NMR spectrum of compound *II* ($n = 6$, R = H), mainly in its vinylic proton maximum[1].



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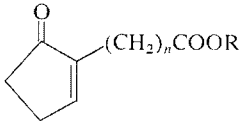
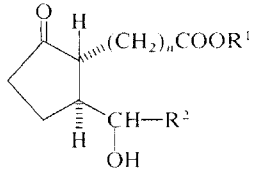


IIa; $n = 5$, R = CH_3
IIb; $n = 5$, R = C_2H_5
IIc; $n = 6$, R = CH_3
IId; $n = 6$, R = C_2H_5
IIe; $n = 10$, R = CH_3



IIIa; $n = 5$, $R^1 = CH_3$, $R^2 = C_4H_{15}$
IIIb; $n = 5$, $R^1 = C_2H_5$, $R^2 = C_5H_{11}$
IIIc; $n = 5$, $R^1 = C_2H_5$, $R^2 = C_6H_{13}$
IIId; $n = 6$, $R^1 = CH_3$, $R^2 = C_4H_{15}$
IIIe; $n = 10$, $R^1 = H$, $R^2 = C_5H_7$
IIIf; $n = 10$, $R^1 = CH_3$, $R^2 = C_5H_7$

Primary alcohols with higher alkyls[7] were added to the prepared ω-(2-oxo-5-cyclopentenyl)alkanoates *II* under the conditions of radical reaction. The addition was catalysed with ditert-butyl peroxide. Under the conditions of procedure *B* fresh portions of the catalyst were added at certain time intervals to the reaction mixture cooled below the boiling point of the alcohol; when the catalyst is added all at once the yield of the product is smaller. After distilling off of the unreacted substances the corresponding homologue *III* was purified chromatographically on a column of alumina or silica gel (acid *IIIe* and esters *IIIb* and *IIIc*). The prepared compounds cannot be distilled without decomposition and they were characterized by IR and ^{1}H-NMR spectra. The supposed structure of all prepared derivatives was proved on the basis of the disappearance of the double bond maximum and appearance of the maximum for the hydroxyl group in the infrared spectrum, as well as by the disappearance of the vinylic proton peak and the presence of the proton on the carbon atom carrying the hydroxyl group in the ^{1}H-NMR spectrum. As expected (steric hindrance,

TABLE I

Alkyl ω-(2-Oxo-5-cyclopentenyl)alkanoates *II*

Starting compound	*II* (yield, %)	B.p., °C/Torr IR spectrum[a]	Formula (mol. weight)	Calculated / Found % C	Calculated / Found % H
Ia	*IIa*	115—117/1	$C_{12}H_{18}O_3$	68·55	8·62
	(48)	1 640, 1 720, 1 750	(210·3)	68·88	9·03
Ib	*IIb*	105—106/0.05	$C_{13}H_{20}O_3$	69·61	8·98
	(50)	1 638, 1 725, 1 750	(224·3)	69·45	8·92
Ic	*IIc*	133—134·5/1·2	$C_{13}H_{20}O_3$	69·61	8·98
	(56)	1 640, 1 720, 1 750[b]	(224·3)	69·47	9·00
Ic	*IIc*[c]	117—122/0·8	$C_{13}H_{28}O_3$	69·61	8·98
	(45·5)	1 640, 1 720, 1 750	(224·3)	69·24	8·95
Id	*IId*	128—132/1	$C_{14}H_{22}O_3$	70·55	8·30
	(50)	1 635, 1 720, 1 745	(238·3)	70·78	9·17
Ie	*IIe*	150—154/0·3[d]	$C_{17}H_{28}O_3$	72·82	10·06
	(50)	1 635, 1 700, 1 735	(280·4)	73·18	10·27

[a] Frequencies of bands in cm^{-1}; [b] measured as liquid: 1635, 1710 and 1745 cm^{-1}, literature[1] gives 1630, 1695 and 1730 cm^{-1} (liquid). The ^{1}H-NMR spectrum was measured at 60 MHz in deuteriochloroform using tetramethylsilane as reference. For the vinylic proton a weakly split triplet was observed with the maximum at $\delta = 7{\cdot}28$. Literature[1] gives $\delta = 7{\cdot}31$; [c] prepared by triple distillation of the crude bromo derivative under reduced pressure; [d] m.p. 39°C.

TABLE II

^{1}H-NMR Spectrum of Substances *III* in δ-Values

Compound	$-CH_3$	$-CH_2-CH_2-$	$-CH_2-CO-$	$-OCH_3$	$-\underset{\vert}{CH}-O$	$-O-CH_2-$
IIIa	0·74—0·98	1·08—1·96	2·00—2·42	3·62	3·58—3·68	—
IIIb	0·82—1·01	1·13—2·00	2·03—2·40	—	3·57—3·77	4·00—4·25
IIIc	0·82—1·02	1·08—2·10	2·61—2·42	—	3·60—3·90	4·04—4·30
IIId	0·72—0·80	0·82—1·98	2·00—2·38	3·64	3·58—3·68	—
IIIe	0·76—1·06	1·08—2·00	2·00—2·60	—	3·65—3·94	—
IIIf	0·74—1·07	1·09—1·98	2·04—2·42	3·65	3·62—3·71	—

primary alcohol) the yields of the reaction are low (10–25%), but the method enables a relatively easy preparation of hydroxyketo esters of acids of the type *III*, representing derivatives of prostanoic acid homologues. The racemic methyl ester of 9-oxo-13-hydroxyprostanoic acid (*IIId*) is closest in its structure to natural prostanoic acid derivatives[8], prostaglandins of series E. For the mutual position of the chains on the cyclopentane ring of the prepared substances *III* a *trans*-configuration can be supposed according to the steric reaction conditions and the analogy with ionic reactions[1,9].

EXPERIMENTAL

The infrared spectra were measured in chloroform solution on a Zeiss UR-10 spectrophotometer, and the ^{1}H-NMR spectra on a Varian 150 instrument at 100 MHz, in deuteriochloroform with tetramethylsilane as internal reference. The purity of the products was checked by thin layer chromatography on alumina (activity II, chloroform as eluent, detection with iodine vapours) or on silica gel G (eluent chloroform–ether (4 : 1), detection with 10% sulfuric acid with 1% ceric

TABLE III

Alkyl ω-[5-(1-Hydroxyalkyl)-2-oxocyclopentyl]alkanoates *III*

Substance (yield, %)	Procedure[a] (time)[b] temperature[c]	Molar ratio of substances *II*: RCH_2OH: catalyst	IR Spectrum cm^{-1}
IIIa (14)	*A* (8) 160–170	1 : 15 : 0·25	1 732, 3 460
IIIb (19·5)	*A* (12) 155–160	1 : 20 : 0·5	1 728, 3 480
IIIc (28·5)	*A* (10) 160–170	1 : 20 : 0·5	1 725, 3 500
IIId (20)	*A* (8) 175–185	1 : 20 : 0·5	1 732, 3 450
IIIe[d] (11)	*B* (8) 150–160	1 : 20 : 0·25	1 710, 3 400
IIIf[e] (22)	*B* (8) 145–155	1 : 20 : 0·25	1 732, 3 450

[a] Procedure *A* is suitable for the addition of alcohols with b.p. over 140°C, procedure *B* for alcohols with b.p. below 140°C; [b] total time of heating in hours; [c] temperature of the bath in °C; [d] for addition acid *II* was used ($n = 10$, R = H), prepared on alkaline hydrolysis of ester *IIe*. The acid was used for reaction undistilled, dried over P_2O_5 at 0·2 Torr for 6 hours; [e] methyl ester *IIIf* was hydrolysed by two hours' refluxing with 20 ml of 10% potassium hydroxide, and the isolated acid had its IR and ^{1}H-NMR spectrum identical with acid *IIIe*.

sulfate and heating). The solvents were evaporated on rotatory evaporator under reduced pressure (water pump). The substances were dried at 20°C and 0·1—0·2 Torr for 6—8 hours. The solutions were dried over anhydrous magnesium sulfate.

Alkyl ω-(2-Oxo-5-cyclopentenyl)alkanoates *II*

0·1 mol of alkyl ω-(2-oxocyclopentyl)alkanoate[5] *I* was added to a solution of 0·12 mol of lead tetraacetate in 480 ml of dichloromethane cooled at −10°C under stirring, followed by a dropwise addition over 2 hours of a solution of 0·48 mol of acetyl bromide in 240 ml of dichloromethane, keeping the temperature of the mixture below 0°C. The mixture was then stirred at this temperature until the lead tetraacetate had reacted completely (2—3 hours). When the temperature of the mixture rose to 20°C, 600 ml of water were added and after 30 minutes' stirring the organic layer was separated, washed with water, saturated sodium hydrogen carbonate solution and water. After drying and evaporation of the solvent 0·3 mol of triethylamine were added to the residue or also dimethylaniline in 250 ml of ether or 150 ml of benzene (in the case of the preparation of compound *IIa*). After 3 hours' heating under reflux the solvent and excess amine were distilled off, the residue was dissolved in 150 ml of ester and the solution washed with water, 25% acetic acid, saturated sodium hydrogen carbonate solution and again water. After drying of the solution and distilling off of ether the residual product was purified by fractional distillation under reduced pressure. The yields, elemental analyses and physical constants of compounds *II* are listed in Table I. The ^{1}H-NMR spectra of all homologues (Table II) were similar and within the following limit values of δ: 1·05—1·90 (—CH_2), 1·95—2·70 (—CH_2CO—), 3·62 (—OCH_3), 7·17—7·40 (—C=CH—).

Alkyl ω-[5-(1-Hydroxyalkyl)-2-oxocyclopentyl]alkanoate *III*

A) A mixture of 0·01—0·02 mol of alkyl ω-(2-oxo-5-cyclopentenyl)alkanoate *II*, a primary alcohol and ditert-butyl peroxide in a 1 : 5 : 0·25—0·5 ratio was added dropwise over 6—10 hours to a 10—15 fold molar excess of alcohol. The addition was carried out under stirring at 140 to 185°C bath temperature (Table III), and under nitrogen or argon. The mixture was stirred at the same temperature for 2 hours and then evaporated. The distillation residue was purified by column chromatography (diameter 20 mm) using a 35 fold amount (weight) of alumina of activity II (first solvent was benzene, followed by chloroform–benzene 1 : 1), or — for substances *IIIb* and *IIIc* — a 30 fold amount of silica gel L (100/160 μ), using benzene and benzene–chloroform 3 : 2 mixture for elution. Substances *III* were oils the spectra of which were measured after drying. The measured values and the yields and the reaction conditions are presented in Table II.

B) In a pressure vessel with a glass insert a mixture of ester or acid *II*, a 20 fold molar amount of the corresponding alcohol, and 1/4 of the total amount of ditert-butyl peroxide were heated. At 75 minute intervals the vessel, which was heated at 145—160°C during this time, was cooled and another portion of the catalyst was added in the form of a 10% solution in the alcohol used. After the addition of the last portion the mixture was heated for another 1·5—2·5 hours. Benzene was then distilled off and the residue worked up as under *A*. In the case of the addition to free acid *II* (R = H) chromatography was carried out on silica gel Ch (100—250 μ).

Elemental analyses were carried out in the Laboratory for Elemental Analyses (head Dr L. Helešic), Department of Organic Chemistry, Institute of Chemical Technology, Prague. The spectra were measured in the Laboratory of NMR spectroscopy of the same Department (head Dr P. Trška) and in the Laboratory of Absorption Spectroscopy, (head Professor B. Hájek) Institute of Chemical Technology, Prague.

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