THE SYNTHESIS OF CYCLOPENTANE DERIVATIVES WITH A RELATION TO PROSTANOIC ACID

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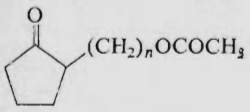
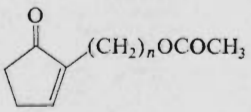
A synthesis of 2-(ω-acetoxyalkyl)-2-cyclopenten-1-ones *II* was worked out. By radical addition of alkanoic acids to cyclopentenones *II* and to esters of ω-(2-oxo-5-cyclopentenyl)-alkanoic acids *III* 2-[3-oxo-2-(ω-acetoxy-alkyl)cyclopentyl]alkanoic acids *V* and/or esters of ω-[5-(1-carboxy-alkyl)-2-oxocyclopentyl] alkanoic acids *IV* were prepared. The homologues and norderivatives of prostanoic acid prepared were isolated by preparative chromatography on silica gel and their ^{1}H-NMR and IR spectra measured.

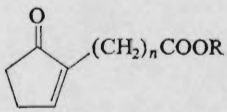
In the last paper of the series of the studies on the syntheses of derivatives and homologues of prostanoic acid, the synthesis of the esters of ω-5-(1-hydroxyalkyl)-2-oxocyclopentyl alkanoic acids was described, that acids were prepared by radical addition of n-alkanols to the esters of ω-(2-oxo-5-cyclopentenyl)alkanoic acids[1]. In this paper the addition of aliphatic acids to substituted cyclopentenones *II* and *III* under the conditions of radical reaction is investigated, with the aim of obtaining new analogues of prostanoic acid.



Ia: n = 2
Ib: n = 5
Ic: n = 6
Id: n = 8
Ie: n = 11



IIa: n = 2
IIc: n = 6
IId: n = 8
IIe: n = 11

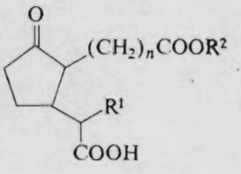


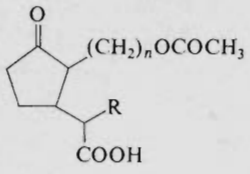
IIIa: n = 5, R = C_2H_5
IIIb: n = 6, R = CH_3

Of the intermediates *II* and *III*, the homologue *IIa* prepared[2] on alkylation of the potassium salt of alkyl cyclopentanonecarboxylate with 2-bromoethyl acetate, hydrolysis and decarboxylation of the alkyl derivative is the lowest. The double bond was introduced by bromination of the corresponding enol acetate (prepared from ketone on reaction with acetic anhydride) with N-bromosuccinimide and de-

hydrobromination under heating with lithium carbonate and pyridine. A simpler method of preparation of compound *IIa* consists in the addition of cyclopentanone to vinyl acetate and introduction of the double bond, and it represents a part of a patent application[3]. The general method of preparation of 2-(ω-acetoxyalkyl)-2-cyclopenten-1-ones, described here, has also been registered for patenting[4]. Unsaturated keto esters *III* were prepared in the described manner[1] or by the method *A* described here, using the reaction of the corresponding ketones with cupric bromide and subsequent dehydrobromination with pyridine, giving a 50% yield. The starting acetoxyalkylcyclopentanones *I*, used for the synthesis of compounds *II*, were synthetized by radical addition of cyclopentanone to alkenol acetates with a terminal double bond. Among the saturated homologues prepared, the adduct, *Ie* prepared in a similar manner[5], is known.

The addition of alkane acids to 2-(ω-acetoxyalkyl)-2-cyclopenten-1-ones *II* in the presence of ditert-butyl peroxide as a radical source and at 130–170°C gives corresponding addition compounds, 2-[(ω-acetoxalkyl)-3-oxocyclopentyl]alkanoic acids *V*. As the main reaction product *trans* derivatives were isolated as less polar compounds. In this manner new cyclopentane derivatives with a skeleton analogous to 9-oxoprostanoic acid, containing different numbers of carbons in the side chains, were prepared. Instead of the carboxyl on carbon atom 2 in the skeleton of prostanoic acid the acetoxy group is attached, and the acid nature of the molecule is due to the carboxyl group on carbon atom 13. After the addition reaction of alkanoic acids to the esters of ω-(2-oxo-2-cyclopentenyl)alkanoic acid *III* the esters of trans-ω-[5(1-carboxyalkyl)-2-oxocyclopentyl]alkanoic acids *IV* were isolated in a similar manner. Thus new analogues of prostanoic acid were again formed, also having a carboxyl group on the carbon atom 13.





IVa: n = 5, $R^1 = CH_3$, $R^2 = C_2H_5$
IVb: n = 5, $R^1 = C_5H_{11}$, $R^2 = C_2H_5$
IVc: n = 6, $R^1 = C_7H_{15}$, $R^2 = CH_3$

Va: n = 6, $R = C_5H_{11}$
Vb: n = 6, $R = C_7H_{15}$
Vc: n = 11, $R = CH_3$
Vd: n = 2, $R = C_{12}H_{25}$

Compounds *IV* and *V* have the carbonyl group in the cyclopentane ring on a site, that is characteristic in natural derivatives of prostanoic acid, in prostaglandins of the E type. Homologue *IVc* represents a 11-deoxy-13-carboxy analogue of prostaglandin E_1. The structure of the derivatives *IV* and *V* prepared was confirmed by spectro-

scopic disappearance of the double bond absorption and the appearance of absorption for the hydroxyl of the carbonyl group in the infrared spectra, and in the case of the ^{1}H-NMR spectra by the disappearance of the triplet for the vinyl proton and appearance of the carbonyl group proton. The low yield of the substances prepared is compensated for by the simplicity of the procedure and its general application. The method of preparation of the substances *IV* and *V* mentioned has been submitted to patenting[6,7].

For the preparation of enone derivatives *II* the methods more or less known from the preparations of other compounds were modified. They consisted in the bromination and debromination with N-bromosuccinimide, with cupric bromide[8] and direct bromination in the presence of mercuric oxide[9] and dehydrobromination with lithium carbonate and pyridine[2] or with triethylamine in benzene[1] were also tested. Cupric bromide seems most convenient, since the cuprous bromide formed in the reaction can be easily converted with bromine to the original cupric salt.

EXPERIMENTAL

The infrared spectra were measured in chloroform solution on a Zeiss UR-10 spectrophotometer tetramethylsilane as internal standard. The purity of the products from preparative column chromatography was checked by thin-layer chromatography on silica gel G (solvent: chloroform–ether 5 : 1; detection: 10% sulfuric acid with 1% of cerium-IV sulfate and heating). The solutions were dried over anhydrous magnesium sulfate and the solvents were distilled under reduced pressure (water pump) on a rotatory evaporator.

2-(ω-Acetoxyalkyl)cyclopentanone *I*

A mixture of ω-alken-1-yl acetate, cyclopentanone and ditert-butyl peroxide in a 1 : 5 : 0·2 ratio was added dropwise over 5 to 6 h and under nitrogen to a stirred 10fold amount (per starting acetate) of boiling cyclopentanone. The mixture was refluxed for 2 h and the decomposition products of the catalyst, the excessive cyclopentanone and the unreacted alkenyl acetate were distilled off through a Vigreux column. The residue was submitted to rectification under reduced pressure. The ^{1}H-NMR spectra are given in Table I. The yields, elemental analyses and the physical constants of compounds *I* are collected in Table II.

2-(ω-Acetoxyalkyl)-2-cyclopenten-1-one *II*

A) A suspension of 0·21 mol of cupric bromide in a solution of 0·1 mol of 2-(ω-acetoxyalkyl)-cyclopentanone in 150 ml of chloroform or dichloromethane with 10% of ethyl acetate was refluxed under stirring and under nitrogen for 4 h. During the reaction hydrogen bromide developed, the elimination of which was facilitated by the introduced nitrogen. Cuprous bromide was filtered off and 0·3 mol of lithium carbonate were added to the filtrate. The solvent was then distilled off at 40°C under reduced pressure. The residue was dissolved in 150 ml of pyridine and the mixture heated at 100°C for 60—100 min in a nitrogen stream under heating and stirring. It was then concentrated in a vacuum to 80 ml, an equal amount of dichloromethane was added and the solution was poured into 300 ml of a saturated sodium chloride solution. The aqueous layer was extracted three times with 80 ml of dichloromethane, the combined extracts were washed

with 50 ml of a saturated sodium chloride solution and dried over magnesium sulfate. After elimination of the solvent the residue was chromatographed on 600 g of silica gel (100/160 μm) with a chloroform–benzene mixture. In the case of lower homologues the product was purified by fractional distillation under reduced pressure, using a column with rotating teflon band. Cyclopentanes *IIa* and *IIc* were prepared in this manner in 25 and 57% yields, respectively.

B) N-Bromosuccinimide (0·1 mol) and dibenzoyl peroxide (0·02 g) or azobis(isobutyronitrile) were added to a solution of 0·1 mol of 2-(ω-acetoxyalkyl)cyclopentanone *I* in 100 to 200 ml of tetrachloromethane and the mixture was stirred and heated under nitrogen for 20 to 60 min. After cooling the separated succinimide was filtered off and washed with tetrachloromethane. Lithium carbonate (0·18 mol) was added to the combined tetrachloromethane solutions and the solvent was distilled off. The mixture was then heated in pyridine as described under *A*. In this manner cyclopentanones *IIa*, *IIc* and *IIe* were prepared in 53, 64·5 and 42% yields, respectively

C) A solution of 0·03 mol of bromine in 30 ml of tetrachloromethane was added to a solution of 0·025 mol of 2-(8-acetoxyoctyl)cyclopentanone in 40 ml of tetrachloromethane in which 0·05 mol of mercuric oxide was suspended and the mixture was refluxed for 20 min. After cooling and filtration the precipitate on the filter was washed with tetrachloromethane and the combined filtrates were evaporated at 40°C on a rotatory evaporator under reduced pressure. The residue was mixed with a solution of 0·1 mol of triethylamine in 50 ml of benzene and the mixture was refluxed for 3 h. The solvent and the excess of triethylamine were distilled off and the residue was mixed with 100 ml of ether and 50 ml of water. After shaking the ethereal layer was washed twice with water and dried over magnesium sulfate. After evaporation of the solvent the residue

TABLE I

^{1}H-NMR Spectra of compounds *II*, *IV* and *V* (in δ-values)

Compound	CH_3	$-CH_2-CH_2-$	$-CO-CH_3$[a] $(-CH_2-CO-)$[a]	$-CH_2-$[b]	$-O-CH_2$ $(-OCH_3)$	$-COOH$[a] $(-C=CH-)$[c]
Ia	—	—	2·07	1·20—2·30	4·09—4·22	—
IIa	—	—	2·04	2·30—2·90	4·12—4·25	(7·18—7·25)
IIc	—	1·16—1·84	2·03	2·08—2·70	3·95—4·12	(7·20—7·34)
IId	—	1·07—1·80	1·92	2·04—2·68	3·94—4·11	(7·18—7·32)
IIe	—	0·95—1·75	2·02	2·07—2·65	3·93—4·13	(7·15—7·30)
IVa	1·10—1·44	1·44—1·77	(2·12)	2·46—2·78	4·02—4·28	8·38
IVb	0·82—1·03	1·03—1·82	(1·92)	2·01—2·53	3·99—4·25	9·97
IVc	0·66—1·02	1·02—1·81	(1·95)	2·08—2·46	(3·66)	9·26
Va	0·75—1·05	1·05—1·84[b]	2·07	1·84—2·49	3·93—4·17	9·10
Vb	0·87—1·15	1·15—1·95[b]	2·18	1·95—2·57	4·01—4·29	9·10
Vc	1·17	1·19—1·45	2·04	1·78—2·71	3·96—4·14	9·20
Vd	0·70—1·04	1·04—1·50	2·02	1·50—2·52	3·94—4·28	9·56

[a] Mean value of a distinct signal; [b] also contains a signal for the protons $-CH_2-CO-$ in the cyclopentane ring; [c] triplet of the vinyl proton[10].

was chromatographed on 150 g of silica gel (100/160 μm), using a mixture of chloroform and benzene (4 : 7) for elution. Yield, 49·4% of 2-(8-acetoxyoctyl)-2-cyclopenten-1-one.

The boiling point temperature of the substance prepared, their elemental composition and the infrared spectra are surveyed in Table II (from all the procedures). The ^{1}H-NMR spectra are presented in Table I.

Esters of ω[5-(1-Carboxyalkyl)-2-oxocyclopentyl]alkanoic Acids *IV*

A mixture of 0·1 mol of ω-(2-oxo-5-cyclopentyl)alkanoic acid ester *III*, a part of the corresponding aliphatic acid (about 1/3 of the total amount) and ditert-butyl peroxide was added dropwise

TABLE II
Cyclopentane derivatives *I* and *II*

Compounds (yield,%) method	B.p., °C/Pa IR spectrum, cm^{-1}	Formula (mol. weight)	Calcul./Found	
			% C	% H
Ia	74·5—75/33[a]	$C_9H_{14}O_3$	63·51	8·29
(17)	1 250, 1 733, 2 980	(170·2)	63·70	8·45
Ib	99/40	$C_{12}H_{20}O_3$	67·89	9·50
(29·5)	1 240, 1 730, 2 935	(212·3)	67·57	9·47
Ic	115—117/27	$C_{13}H_{22}O_3$	68·99	9·80
(68·7)	1 242, 1 730, 2 930	(226·3)	68·73	9·96
Id	124—125/27	$C_{15}H_{26}O_3$	70·85	10·28
(54·0)	1 240, 1 730, 2 935	(254·3)	70·49	10·30
Ie	148—150/40[b]	$C_{18}H_{32}O_3$	72·93	10·88
(63·5)	1 245, 1 730, 2 930	(296·4)	72·92	10·87
IIa	74—75/13	$C_9H_{12}O_3$	64·27	7·19
(25)[c]	1 640, 1 705, 1 740	(168·2)	64·46	7·35
A	2 930, 2 970, 3 020			
IIc	148/106	$C_{13}H_{20}O_3$	69·61	8·99
(57)[d]	1 632, 1 695, 1 730	(224·3)	69·43	9·09
A	2 870, 2 940, 3 010			
IId	124—125/13	$C_{15}H_{24}O_3$	71·39	9·59
(49·4)	1 642, 1 695, 1 728	(252·3)	70·71	9·65
C	2 855, 2 925, 3 000			
IIe	160—165/27	$C_{18}H_{30}O_3$	73·43	10·27
(42)	1 630, 1 690, 1 722	(294·4)	73·15	10·44
B	2 860, 2 920, 3 005			

[a] Prepared according to ref.[3]; [b] in ref.[5] b.p. 158°C/1 mm Hg; [c] method B gave a 53% yield, purity 90%; [d] method B gave a 64·5% yield.

and under stirring, over 7 to 8 h, to the remaining 2/3 of the total amount of the aliphatic acid (for the ratio of substances see Table II) kept under a nitrogen stream. The temperature of the addition was 160°C. (In the case of the reaction with propionic acid the reaction was carried out at the propionic acid boiling temperature). After addition of the mixture of substances the heating was continued for another 2 to 3 h and the excess of the aliphatic acid and the unreacted cyclopentanone *III* were distilled off gradually. The residue was dissolved in 150 ml of ether and extracted with three 50 ml portions of saturated hydrogen carbonate solution. The aqueous alkaline extract was washed with 100 ml of ether, then acidified with 10% hydrochloric acid and the product was extracted with ether. The ethereal extract was washed with water, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed on a silica gel column (300 g, 100—160 μm) with a benzene–chloroform mixture with increasing concentration of chloroform. A mixture of 20% of benzene in chloroform eluted the more polar fraction containing the pure product with the *trans* configuration. The purity of the product was checked by thin layer chromatography. The solvent was eliminated from the fraction and the product was dried at 50°C and 13—27 Pa for 10 h. Yields, elemental analyses and infrared spectra are presented in Table III and the ^{1}H-NMR spectra in Table I.

TABLE III
Cyclopentane derivatives *IV* and *V*

Starting compound RCOOH	Product[a] (yield, %)	Starting compound : RCOOH : catalyst[b] (eluent C_6H_6 : $CHCl_3$)[c]	Formula (mol. weight)	Calcul./Found	
				% C	% H
IIIa	*IVa*	1 : 15·8 : 0·33	$C_{16}H_{26}O_5$	64·40	8·78
R = C_2H_5	(15)	(1 : 4)	(298·4)	64·27	9·09
IIIa	*IVb*	1 : 10 : 0·2	$C_{20}H_{34}O_5$	67·74	9·47
R = C_6H_{13}	(10)	(1 : 4)	(354·5)	67·76	9·67
IIIb	*IVc*	1 : 10 : 0·2	$C_{22}H_{38}O_5$	69·07	10·01
R = C_8H_{17}	(5)	(1 : 4)	(382·5)	69·43	9·98
IIc	*Va*	1 : 20 : 0·15	$C_{20}H_{34}O_5$	67·74	9·47
R = C_6H_{13}	(17·8)	(1 : 1)	(354·5)	67·94	9·42
IIc	*Vb*	1 : 15 : 0·14	$C_{22}H_{38}O_5$	69·07	10·01
R = C_8H_{17}	(9·2)	(1 : 4)	(382·5)	68·58	9·73
IIe	*Vc*	1 : 20 : 0·5	$C_{20}H_{34}O_5$	67·74	9·47
R = C_2H_5	(9·6)	($CHCl_3$)	(354·5)	67·39	9·51
IIa	*Vd*	1 : 10 : 0·2	$C_{23}H_{40}O_5$	69·66	10·17
R = $C_{13}H_{27}$	(9·0)	(1 : 9)	(396·6)	69·28	9·81)

[a] Infrared spectra of compounds *IV* displayed bands in the following ranges: 1 705—1 710, 1 720—1 730, 3 500 and 3 600 weak . cm^{-1}, and those of compounds *V* in the ranges 1 710, 1 730—1 740, 3 000 cm^{-1}; [b] molar ratio; [c] ratio of solvents, at which the pure product was withdrawn.

2-[3-Oxo-2-(ω-acetoxyalkyl)cyclopentyl]alkanoic Acids *V*

A mixture of 2-(ω-acetoxyalkyl)2-cyclopenten-1-one, a part of the aliphatic acid and ditert-butyl peroxide (in a molar ratio given in Table III) was added dropwise over 5—6 h to the stirred second part of the aliphatic acid, kept at 160—170°C. The ratio of the acid added dropwise to the second part was usually 2 : 3. When propionic acid was used the reaction took place at its boiling point. In the preparation of compound *Vd* a mixture of cyclopentanone *IIa* with the catalyst was added in parts to the melted myristic acid, at 1 h intervals. The heating was continued for another 2 h and the excess of the aliphatic acid and the unreacted compound *II* were evaporated under reduced pressure. The residue was dissolved in ether and the acid fraction purified by extraction with 10% sodium carbonate solution, washing of the aqueous alkaline fraction with ether and acidification, similarly as in the preparation of compounds *IV*. The product was extracted with ether, washed with water and dried over magnesium sulfate. After evaporation of the solvent the residue was chromatographed on a 25—40 fold amount of silica gel (100 to 160 μm), using a mixture of benzene and chloroforom as eluent. After separation of the fractions which contained the starting compounds and a small amount of the *cis* isomer, the *trans* isomer was isolated as the more polar substance. The ratio of the solvents at which pure compounds *V* were collected is given in Table III. The purity of the products was checked by thin-layer chromatography on silica gel, under the conditions given in the introduction. After the elimination of the solvent the products were dried at 49°C and 27 Pa for 10 h. The yields, results of the analyses and the infrared spectra are summarized in Table III, the ^{1}H-NMR spectra in Table I.

The elemental analyses were carried out in the Department of organic analysis, the ^{1}H-NMR *spectra in the Laboratory of* NMR *spectroscopy, and the infrared spectra in the Department of infrared spectroscopy, Prague Institute of Chemical Technology.*

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