THE SYNTHESIS OF KETO ACIDS AND HYDROXY ACIDS AND THEIR ESTERS WITH CYCLOPENTANE RING

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Using radicalic addition of cyclopentanone on unsaturated carboxylic acids or esters with the terminal double bond, *I*, ω-(2-oxocyclopentyl)alkanoic acids or esters *II* have been prepared. The keto esters obtained (and the keto acid *IIa*) were reduced with sodium borohydride to corresponding alkyl ω-(2-hydroxycyclopentyl)alkanoates *III* (or hydroxy acid *IIIa*). The infrared spectra of the compounds prepared have been measured.

On the basis of known facts on the structure and physiological activity of prostaglandins and their analogues[1-3], and experiences with the utilization of radical additions for the synthesis of derivatives of unsaturated hydroxy acids[4,5], some compounds have been synthetized which are similar in structure to prostaglandins of the series E and F, and their homologues. First derivatives of cyclopentanone were prepared, having an alkyl chain in the α-position to the carbonyl group, with the carboxyl group at the end of the chain. After addition of cyclopentanone to unsaturated acids and esters *I* in the presence of an initiator 6-(2-hydroxycyclopentyl)-hexanoic acid (*IIa*), methyl 6-(2-oxocyclopentyl)hexanoate (*IIb*), ethyl 6-(2-oxocyclopentyl)hexanoate (*IIc*), methyl 7-(2-oxocyclopentyl)heptanoate (*IId*), ethyl 7-(2-oxocyclopentyl)heptanoate (*IIe*), methyl 9-(2-oxocyclopentyl)nonanoate (*IIf*), and methyl 11-(2-oxocyclopentyl)undecanoate (*IIg*) were isolated. Esters *II* were hydrolysed with alkali to acid *II* (R = H) and their physical constants were compared with some acids described earlier[5,6].

The addition of cyclopentanone to unsaturated esters *I* takes place with relative ease, best yields (up to 70%) having been obtained in the reaction where ditert-butyl peroxide was used as catalyst, while lower ones were observed when dibenzoyl peroxide and ultraviolet light were applied. In Table I one example of each of the last mentioned methods of initiation are given as illustration. In order to prevent the formation of higher telomers the reaction was carried out in excess cyclopentanone.

Reduction of the prepared esters of ω-(2-oxocyclopentyl)alkanoic acids *II* and acid *IIa* with sodium hydride at 0°C gave corresponding esters of ω-(2-hydroxycyclopentyl)alkanoic acids (and acid *IIIa*) to which the prevailing (about 70%) configura-

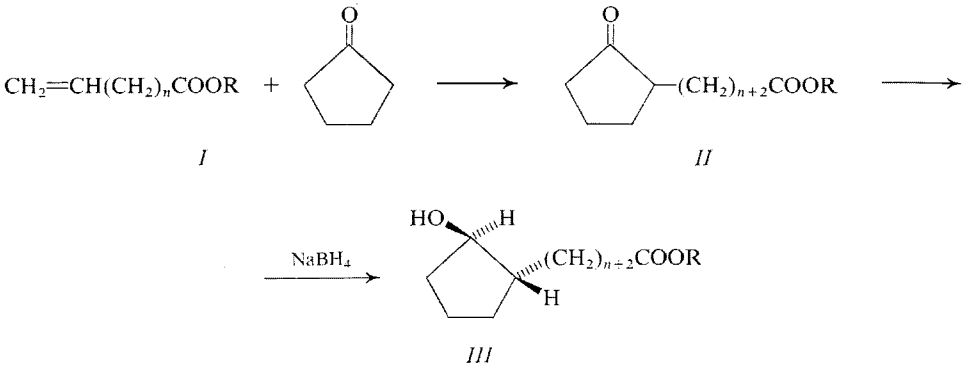
tion *trans* (*III*) was assigned on the basis of their synthesis and comparison with similar reactions[6,7]. Using this method (which has been already described[8]) methyl 6-(2-hydroxycyclopentyl)hexanoate (*IIIb*), ethyl 6-(2-hydroxycyclopentyl)hexanoate (*IIIc*), methyl 7-(2-hydroxycyclopentyl)heptanoate (*IIId*), ethyl 9-(2-hydroxycyclopentyl)nonanoate (*IIIf*) and methyl 11-(2-hydroxycyclopentyl)undecanoate (*IIIg*) were prepared. Using a similar reduction of keto acid *IIa* 6-(2-hydroxycyclopentyl)-hexanoic acid (*IIIa*) was prepared which was characterized as methyl ester *IIIb* after esterification with diazomethane. The reduction of the esters and the acid took place in 80–90% yield. Transesterification of methyl ester *IIIb* to ethyl ester *IIIc*, and esterification of acid *IIIa* to ethyl ester *IIIc* were also carried out, but it is more suitable to prepare ethyl ester *IIIc* on reduction of ethyl ester *IIc*. The purity of the isolated hydroxy esters *III* was controlled by thin layer chromatography on alumina

TABLE I

Alkyl ω-(2-Oxocyclopentyl)alkanoates and ω-(2-Oxocyclopentyl)alkanoic Acids *II*

Product (yield, %)	Initiator[a] time[b]	B.p., °C/Torr IR spectrum cm^{-1}	Formula (m.w.)	Calculated/Found	
				% C	% H
IIa	T	130–133/0·02	$C_{12}H_{18}O_3$	66·64	9·15
(25)	6	—	(198·3)	67·16	9·11
IIb	T	124–125/0·5	$C_{12}H_{20}O_3$	67·90	9·50
(70)	7	1 735	(212·3)	68·05	9·50
IIc	T	93–96/0·15	$C_{13}H_{22}O_3$	69·00	9·80
(68)	8	1 730	(226·3)	69·36	9·83
IIc	U	115–117/0·4	$C_{13}H_{22}O_3$	69·00	9·80
(21)	8	1 730	(226·3)	69·28	9·97
IId	T	110–111/0·8	$C_{13}H_{22}O_3$	69·00	9·80
(42·5)	9	1 750	(226·3)	69·12	9·64
IIe	D	125–129/0·4	$C_{14}H_{24}O_3$	69·96	10·07
(23)	8	1 740	(240·3)	70·24	10·28
IIe	T	125–126/0·3	$C_{14}H_{24}O_3$	69·96	10·07
(35)	8	1 740	(240·3)	70·05	10·25
IIf	T	125/0·15	$C_{16}H_{28}O_3$	71·61	10·51
(67)	8·5	1 735	(268·4)	71·64	10·48
IIg	T	154–160/0·45	$C_{17}H_{30}O_3$	72·30	10·71
(53)	8·5	1 735	(282·4)	72·29	10·84

[a] T tert-butyl peroxide, U ultraviolet radiation, D dibenzoyl peroxide; [b] Total heating time in hours.



I *II* *III*

a: $n = 3$, R = H
b: $n = 3$, R = CH_3
c: $n = 3$, R = C_2H_5
d: $n = 4$, R = CH_3
e: $n = 4$, R = C_2H_5
f: $n = 6$, R = C_2H_5
g: $n = 8$, R = CH_3
h: $n = 4$, R = H
i: $n = 6$, R = H
j: $n = 8$, R = H

or silica gel. In the infrared spectra of hydroxy esters *III* maxima between 3400 and 3500 cm^{-1} appear. In the ^{1}H-NMR spectrum a signal at $\delta = 3{\cdot}8$ is present which was assigned to the proton on the carbon atom carrying the hydroxyl group.

Of the substances prepared in this study keto acid *IIh* and dinitrophenylhydrazone of ethyl ester *IId* have been described in literature[6]. Keto acid *IIh* was prepared by alkylation of ethyl cyclopentanonecarboxylate with ethyl 7-bromoheptanoate, followed by hydrolysis and decarboxylation. The keto acid was used as starting material for the synthesis of a prostaglandin derivative[6]. Among other homologues of substances *II* keto acid *IIj* is known, which was prepared on addition of cyclopentanone to undecylenoic acid[5] and from chaulmoogroic oil[9]. From the same oil hydroxy acid *IIIj* was also prepared in mixture with another isomeric acid[9].

From keto esters *II* and hydroxy esters *III* (hydroxy acids *III* were not isolated) corresponding acids were prepared by alkaline hydrolysis, and from them sodium salts. Sodium salts and esters of some homologues of substances *II* and *III* were submitted to some pharmacological tests in collaboration with the Gentili firm (Pisa, Italy), and the Department of Pharmacology, Medical Faculty, Charles University (Hradec Králové, Czechoslovakia), mainly that for stomach secretion. The results of these tests have been published elsewhere[10].

EXPERIMENTAL

The infrared spectra were measured on a Perkin-Elmer 325 instrument, the ^{1}H-NMR spectra on a Varian XL 100–15 (100 MHz) instrument, in deuteriochloroform with tetramethylsilane as reference. The purity of the products was checked by gas chromatography on Chrom II (Laboratorní přístroje — Prague) and thin layer chromatography on alumina (activity II, eluent chloroform–ether, detection with 10% sulfuric acid containing 1% of ceric sulfate and heating).

The solvents were evaporated on a rotary evaporator under reduced pressure (water pump). The solutions were dried over magnesium sulfate.

Alkyl ω-(2-Oxocyclopentyl)alkanoates and ω-(2-Oxocyclopentyl)alkanoic Acids *II*

A mixture of ester of unsaturated acid *I*, catalyst (one fifth of the molar amount of the ester used), and the remaining part of cyclopentanone was added to four fifths to five sixths of the total amount of cyclopentanone (ten-fold molar amount per the ester or acid *I* used) under stirring and boiling. The mixture was refluxed for 2 hours. After distillation off of the unreacted substances the product was purified by fractional distillation under reduced pressure. In the preparation of compound *IIc* under initiation with ultraviolet light the starting *Ic* mixed with a ten-fold molar amount of cyclopentanone and the same amount of tert-butanol was irradiated with an ultraviolet lamp (250 W) from a 1 cm distance, under refluxing. Yields, total time of heating of the reaction mixture, physical constants and analyses of the prepared substances are listed in Table I.

The prepared esters of keto acids *III* were hydrolysed by two hours' boiling with a 10% sodium hydroxide solution (a triple molar amount). After extraction of the alkaline mixture with ether the aqueous fraction was acidified with 10% hydrochloric acid and the product extracted with ether. After washing the ethereal extract with water, drying and evaporation of the solvent the residue was distilled. The yield, after distillation, was between 40 and 50%. Boiling points, analyses and infrared spectra are given in Table II. From the keto acids *II* (R = H) sodium salts were prepared by dissolution of the acids in an equivalent amount of sodium hydroxide and used for physiological tests.

TABLE II

ω-(2-Oxocyclopentyl)alkanoic Acids *II* (R = H)

Starting ester	Acid (yield, %) b.p., °C/Torr	Formula (m.w.)	Calculated/Found % C	% H	IR spectrum cm^{-1}
IIb	*IIa* (45) 138/0·25	$C_{11}H_{18}O_3$ (198·3)	66·64 66·91	9·15 9·20	1 715, 1 730
IIe	*IIh* (52) 155/0·3	$C_{12}H_{20}O_3$ (212·3)	67·90 68·07	9·50 9·60	1 720, 1 735[a]
IIf	*IIi* (55) 157—160/0·01	$C_{14}H_{24}O_3$ (240·3)	69·96 70·24	10·06 9·88	1 727
IIg	*IIj*(60) 45—46°C[b]	$C_{16}H_{28}O_3$ (268·4)	71·61 72·11	10·52 10·65	1 715, 1 735

[a] IR spectrum from literature[6]; 1 710, 1 725; [b] Melting point, in ref.[5,9] the m.p. is 51—52°C.

Alkyl ω-(2-Hydroxypentyl)alkanoates and ω-(2-Hydroxycyclopentyl)alkanoic Acids *III*

A solution of sodium borohydride (a triple molar excess, of the substance *II*) in 70 ml of icy water was added to a solution of 0·05 mol of keto derivative *II* in 250 ml of 2-propanol under stirring at 0°C to −10°C. The mixture was stirred for 3 hours at the same temperature. Acetone (100 ml) and acetic acid (120 ml) were then added dropwise and the solution concentrated at reduced pressure. The residue was extracted with ether and the extract washed with water, 10% sodium hydrogen carbonate and water, and then dried. After elimination of ether by distillation the residue was distilled. Yields of products were 80–85%.

Boiling points, results of analyses and infrared spectra of the prepared substances are listed in Table III. On thin layer chromatography (alumina act. II, benzene–chloroform, detection with iodine; or, silica gel, chloroform–ether 4 : 1, detection with 10% sulfuric acid with 1% ceric sulfate and heating) the products appeared to be single, the ratio of the distance of the spot of starting substance *II* and of product *III* was higher than one.

For the reduction of free acid *IIa* a three-fold molar excess of sodium borohydride in 40 ml of methanol was added dropwise to a solution of 0·01 mol of the starting substance in 30 ml of methanol and allowed to stand for three hours. Water (10 ml) and 10% hydrochloric acid (10 ml) were then added and the product extracted with ether. The extract was washed with water and dried. After distillation off the solvent hydroxy acid *IIIa* was isolated which was converted with diazomethane to its methyl ester. The identity of this ester with methyl ester *IIIb* prepared by reduction of methyl ester *IIb* was proved by thin layer chromatography and infrared spectra of both substances. In the ^{1}H-NMR spectrum of methyl ester *IIIb* the following signals were present (in δ-values): 1·20–1·50 (—CH_2—), 2·10–2·40 (—CH_2CO—), 3·67 (—OCH_3), 3·80 (—CH—O), 1·94 (at 60°C, —OH).

TABLE III

Alkyl ω-(2-Hydroxycyclopentyl)alkanoates and ω-(2-Hydroxycyclopentyl)alkanoic Acids *III*

Compound (yield, %)	B.p., °C/Torr (IR spectrum cm^{-1})	Formula (m.w.)	Calculated/Found	
			% C	% H
IIIa	157–158/0·01	$C_{11}H_{20}O_3$	65·97	10·07
(42)	(—)	(200·3)	66·21	10·20
IIIb	106–109/0·2	$C_{12}H_{22}O_3$	67·26	10·35
(85)	(1 735, 3 450, 3 620)	(214·3)	67·11	10·40
IIIc	125/0·5	$C_{13}H_{24}O_3$	68·39	10·60
(88)	(1 730, 3 450, 3 625)	(228·3)	68·73	10·69
IIId	110–112/0·2	$C_{13}H_{24}O_3$	68·39	10·60
(85)	(1 750, 3 400, 3 625)	(228·3)	68·74	10·90
IIIf	127–128/0·1	$C_{16}H_{30}O_3$	71·07	11·18
(82)	(1 730, 3 470, 3 610)	(270·4)	71·00	11·16
IIIg	164–167/0·2	$C_{17}H_{32}O_3$	71·79	11·34
(84)	(1 740, 3 460, 3 610)	(284·4)	72·05	11·50

The esters of hydroxy acid *III* were submitted to alkaline hydrolysis, as described in the case of the hydrolysis of ketoesters *II*, with the difference that after the elimination of the solvent the residue was not distilled but dissolved directly in an equivalent amount of sodium hydroxide solution, giving thus a solution of sodium salt of a suitable concentration for physiological tests.

From crude acid *IIIa* ethyl ester *IIIc* was obtained by esterification with ethanol in the presence of *p*-toluenesulfonic acid, b.p. 112—113°C/0·35 Torr, in a 70% yield. Trans-esterification of methyl ester *IIIb* to ethyl ester *IIIc* was carried out by four hours' heating at 50—60°C in ethanol, under catalysis of sodium ethoxide. After the working up of the reaction mixture ethyl ester of b.p. 105°C/0·15 Torr was isolated in a 82% yield. The purity of the ethyl esters from both experiments was controlled on a gas chromatograph.

Elemental analyses were carried out in the Laboratory of Organic Analysis (head Dr L. Helešic), Department of 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 Prof. B. Hájek), Institute of Chemical Technology, Prague. For technical assistance and for the preparation of starting compounds we thank Mr N. Vodeničarov.

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