PREPARATION AND THE CONFIGURATION DETERMINATION OF *cis*-ALKYL ω-(2-HYDROXYCYCLOPENTYL)ALKANOATES*

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Several homologous alkyl ω-(2-hydroxycyclopentyl)alkanoates were prepared by catalytic hydrogenation of alkyl ω-(2-oxocyclopentyl)alkanoates. On the basis of their ^{1}H-NMR spectra it was found that the products have predominantly *cis* (*erythro*) configuration.

During the study of the reduction of ω-(2-oxocyclopentyl)alkanoic acids and their esters with sodium borohydride *trans* (*threo*) configuration has been assigned to the predominating isomer of the corresponding hydroxy ester or hydroxy acid *III* – as described in the first communication of this series[1]. We looked for a method of preparation of the *cis* isomer which we needed for the comparison of its spectra and physiological activities with the *trans* derivative. We chose catalytic hydrogenation under the supposition that after addition of hydrogen to the double bond of the carbonyl of the keto acid or keto ester *I* from the more accessible side, *i.e.* from the side opposite to the substituent, the required *cis* isomer would be formed. Therefore some homologues of alkyl ω-(2-oxocyclopentyl)alkanoates (or alkanoic acid) *I* were hydrogenated on Raney nickel or Adams catalyst in an alcohol corresponding to the ester, or in acetic acid, at 100°C (substance *Id* at 60–80°C) and 100 atm. Corresponding hydroxy esters (or hydroxy acids) *II* were isolated, having predominantly a *cis* configuration. In this manner 6-(2-hydroxycyclopentyl)hexanoic acid (*IIa*), methyl 6-(2-hydroxycyclopentyl)hexanoate (*IIb*), ethyl 6-(2-hydroxycyclopentyl)hexanoate (*IIc*), methyl 7-(2-hydroxycyclopentyl)heptanoate (*IId*), ethyl 7-(2-hydroxycyclopentyl)heptanoate (*IIe*), and methyl 11-(2-hydroxycyclopentyl)-undecanoate (*IIf*) were prepared (Table I). As regards the isolation of the products after hydrogenation of the free acid *I* it is more suitable to convert the crude hydroxy-acid *II* to its ester and then to distill the latter. The distillation of hydroxy acids *II* is

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connected with large losses, especially in the case of higher homologues. The described preparation of hydroxy esters *II* has been registered in the patent literature[2].

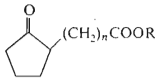
Some homologues of substances of type *II* have already been described in literature, while the configuration of the hydroxyl group has not been indicated. Thus, the ester of hydroxy acid *II*, where $n = 4$ and $R = C_2H_5$, was prepared by reduction of the ethyl ester of the corresponding keto acid with aluminium isopropoxide in isopropyl alcohol[3]. Starting from natural material the hydrogenation of the epoxide prepared from the methyl ester of chaulmoogric and hydnocarpic acid higher homologues of substance *II* were prepared, where $n = 10$ and 12, and $R = H$ and CH_3, in admixture with the 3-hydroxy isomer[4]. Further the above mentioned preparation of substances *II* with predominating *trans* configuration is also known, carried out by reduction of keto acids or their esters of type *I* with sodium borohydride[1]. With ethyl 6-(2-hydroxycyclopentyl)hexanoate (*IIc*) a more detailed study was carried out concerning the relative ratio of both isomers and the proof of their

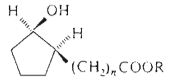
TABLE I
Alkyl ω-(2-Hydroxycyclopentyl)alkanoates *II*

Product[a] Catalyst	B.p., °C/Torr (yield, %)	Formula (m. w.)	Calculated/Found % C	% H	IR Spectrum cm^{-1}
IIa[b]	154–160/0·2	$C_{11}H_{20}O_3$	71·69	10·94	—
Pt	(60)	(184·3)	71·96	10·71	
IIb	129/0·3	$C_{12}H_{22}O_3$	67·26	10·35	1 730, 3 480,
Ni	(87)	(214·3	67·26	10·42	3 620
IIc	114/0·2	$C_{13}H_{24}O_3$	68·39	10·60	1 730, 3 470,
Ni	(90)	(228·3)	68·04	10·63	3 615
IId	130–131·5/0·35	$C_{13}H_{24}O_3$	68·39	10·60	1 730, 3 460,
Ni	(85)	(228·3)	68·07	10·85	3 610
IIe[c]	138–140/0·4	$C_{14}H_{26}O_3$	69·38	10·81	1 730, 3 450,
Pt	(76)	(242·3)	69·51	10·62	3 605
IIf	136–138/0·25	$C_{17}H_{32}O_3$	71·79	11·34	1 725, 3 460,
Ni	(87)	(284·4)	72·18	11·44	3 605

[a] Hydroxy derivative obtained by catalytic hydrogenation of compounds *I*, of predominantly *cis* configuration; [b] product *IIa* was prepared by hydrogenation of keto acid *Ia*. Using diazomethane its methyl ester of b.p. 126–129°C/0·3 Torr was prepared, its IR spectrum was identical with that of compound *IIb*; [c] ethyl ester of *IIe* was submitted to alkaline hydrolysis, giving acid of b.p. 165–168°C/0·2 Torr, for $C_{12}H_{22}O_3$ (214·3) calculated: 67·26% C, 10·35% H; found: 67·51% C, 10·47% H.

Ia, n = 5, R = H
Ib, n = 5, R = CH_3
Ic, n = 5, R = C_2H_5
Id, n = 6, R = CH_3
Ie, n = 6, R = C_2H_5
If, n = 10, R = CH_3





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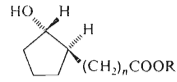


III

configuration. The starting keto ester *Ic*, prepared – similarly as other keto acids *I* – by radicalic addition of cyclopentanone to unsaturated esters or acids with a terminal double bond[1] did in fact give good results according to elemental analysis, but a gas chromatographic analysis showed that it contained about 5% of other substances (evidently isomers in other positions after radicalic addition). Therefore keto ester *Ic* was further purified up to a 99–100% purity, and the *cis* isomer was separated after hydrogenation on a silica gel column. Similarly the *trans* isomer *IIIc*, was also isolated, which was prepared from pure ester *Ic* by reduction with sodium borohydride[1]. It was found that after hydrogenation 74·5% of *cis* isomer *IIc* and 25·5% of *trans* isomer *IIIc* are formed, and that after reduction with the mentioned hydride 27·8% of *cis* isomer and 72·2% of *trans* isomer are obtained. Similar results were obtained on GLC analysis in the case of hydrogenation products and the products of reduction with hydride of substances *IIe*, *IIf* and *IIIe* and *IIIf* (Table III).

The ^{1}H-NMR spectra of both esters *IIc* and *IIIc* differ only by the shift of proton on the carbon atom carrying the hydroxyl group. In isomer *IIc* the signal of this proton appears at 4·10 ppm, while in isomer *IIIc* it is at 3·80 ppm. This difference

TABLE II
^{1}H-NMR Spectrum of Methyl ω-(2-Hydroxycyclopentyl)alkanoates *II* (δ-scale)

Methyl ester	—OH	Triplet for —CH_2CO—	OCH_3	—CH—O
IIb	—[a]	2·31 (*J* = 7·5 Hz)	3·67	4·12
IId	1·78[b]	2·32 (*J* = 7·5 Hz)	3·68	4·12
IIf	1·83[b]	2·31 (*J* = 7·5 Hz)	3·68	4·12

[a] Overlapped by signals of —CH_2—; [b] measured at 60°C.

could be explained by an increased shielding of the proton 1 (Table IV) by the eclipsed C—C bond in the compound with a *trans* configuration[5], and this configuration assigned to compound *IIIc*. In order to verify this assignment a series of measurements was carried out with both isomers using $Eu(dpm)_3$ (tris(2,2,6,6-tetramethylheptanedionato)europium) in the region of the molar ratios $Eu(dpm)_3$: hydroxy ester below 0·63. Limiting induced shifts Δ, defined by the relationship $\delta_i = \Delta_i R_p + \delta_i^0$, where δ_i is the observed shift of the measured proton at molar ratio R_p (molar concentration of the shifting reagent/molar concentration of the compound) and δ_i^0 represents the shift without the reagent, were obtained by the least squares method from the linear dependence of the shift on the R_p value (Table V). Under the sup-

TABLE III
GLC Analysis of Reduction Products

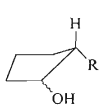
Method of reduction	Hydrogenation			With $NaBH_4$		
Product	c	e	f	c	e	f
Amount of isomer, % *cis II*	75·7	68·2	78·1	23·8	23·7	24·9
Amount of isomer, % *trans III*	24·3	31·8	21·9	76·2	76·3	75·1

	c	e	f
Retention time, min *cis II*	8·48	16·79	14·00
Retention time, min *trans III*	9·22	18·61	15·15
Column temperature, °C	150	140	175

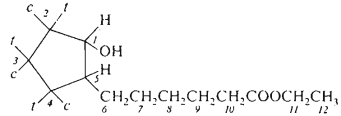
TABLE IV
^{1}H-NMR Spectrum of *cis* and *trans* Ethyl 6-(Hydroxycyclopentyl)-hexanoates

Proton[a]	*trans IIIc*	*cis IIc*
1	3·80 (m)	4·1 (m)
2 to 9	1·1—2·1	1·2—2·1
10	2·29 (t, J = 7·5 Hz)	2·30 (t, J = 7·5 Hz)
11	4·12 (qa, J = 7 Hz)	4·12 (qa, J = 7 Hz)
12	1·25 (t, J = 7 Hz)	1·25 (t, J = 7 Hz)

[a] See formula *V*.



IV



V

position of the prevailing conformation of the cyclopentane ring with the side chain as in formula *IV* we calculated the coordinates of the cyclopentane ring (Table VI). For the value of the limiting induced shift the relationship[6] $\Delta = K \,.\, 3\cos^2\Theta - 1)/r^3$

TABLE V

Limiting Induced Shifts on the Ring

Proton[a]	Δ^{obs} (*trans*)	Δ^{obs} (*cis*)	Proton[a]	Δ^{obs} (*trans*)	Δ^{obs} (*cis*)
1	23·85	23·21	4*c*	6·69	10·80
2*c*	15·91	14·87	4*t*	8·87	5·45
2*t*	10·51	8·67	5*c*	16·69	—
3*c*	8·87	10·80	5*t*	—	8·67
3*t*	6·69	6·52			

[a] See formula *V* where *c*, *t* means *cis* or *trans* position with respect to the hydroxyl group.

TABLE VI

Coordinates of Protons on the Cyclopentane Ring in Å

Proton	*trans* Isomer			*cis* Isomer		
	x	*y*	*z*	*x*	*y*	*z*
1	−1·87	0·00	1·02	−1·87	0·00	1·02
2*c*	−1·44	−1·39	−1·57	−1·66	−1·92	−0·52
2*t*	−2·37	−1·94	−0·19	−3·17	−1·03	−0·58
3*c*	−3·36	−0·54	−2·53	−0·87	−1·01	−2·55
3*t*	−4·29	−1·10	−1·14	−2·61	−0·93	−2·87
4*c*	−3·94	1·55	−1·62	−0·79	1·29	−2·47
4t	−4·03	0·93	0·02	−2·52	1·37	−2·79
5*c*	−1·50	1·39	−1·65		—	
5*t*		—		−3·08	1·35	−0·50

applies in the first approximation, where r is the distance of the lanthanoid and the measured proton and Θ is the angle of the connecting lines lanthanoid–oxygen and lanthanoid–measured proton (O—Ln—H), and K is the proportionality constant. Applying the optimization of the spacial position of the paramagnetic centre and the constant K value for the best agreement of the calculated and the measured values of the limiting induced shifts Δ_i for each configuration, the parameters were obtained which are listed in Table VII. The assignment of the signals in the spectra with the shift reagent was carried out both on the basis of decoupling and – in the case of overlap of several signals – by comparison of the optimization criteria P for various possible assignments ($P = \sqrt{\sum (\Delta_i^{obs} \Delta_i^{calc})^2 / \sum \Delta_i^{obs2}}$, where Δ_i^{obs} and Δ_i^{calc} represented the observed and the calculated limiting induced shifts). It is evident that the largest limiting induced shift – 23·21 and 23·85 – is displayed by the proton H-1 bound directly on the carbon atom carrying the hydroxyl group. The second largest value can be expected for hydrogen atoms on neighbouring carbons, *cis* oriented with respect to the hydroxyl. It follows from Table V that in isomer *IIIc* two such hydrogens are present and Δ is 16·69 and 15·91, while in compound *IIc* a single such hydrogen occurs, with $\Delta = 14{\cdot}87$. This fact confirms the assumption that in isomer *IIIc* the substituents on the cyclopentane ring are mutually *trans* oriented and in compound *IIc* are *cis* oriented. The optimization calculations, which gave for the mentioned assignments of the configuration distinctly best values for the optimization criterion P (Table VII), are also in full agreement with this. For example, for the opposite assignment the P value for derivative *IIIc* increased to 0·179 and for compound *IIc* to 0·21, *i.e.* 3 to four times.

TABLE VII
Calculation of Limiting Induced Shifts, Optimum Case

Proton	*trans* Isomer		*cis* Isomer	
	Δ^{calc}	Δ^{obs}	Δ^{calc}	Δ^{obs}
1	23·56	23·85	23·30	23·21
2*c*	15·14	15·91	13·71	14·87
2*t*	12·43	10·51	8·53	8·67
3*c*	7·78	8·87	11·20	10·80
3*t*	6·90	6·69	6·73	6·52
4*c*	6·85	6·69	11·20	10·80
4*t*	8·07	8·87	6·55	5·45
5*c*	16·99	16·69	—	—
5*t*	—	—	8·23	8·67
P	0·006		0·051	

The determined configuration of compounds *II* is identical with that of the natural compounds – prostaglandins F, and acid *II*, where $n = 6$ and R = H, is in fact a part of the molecule of prostaglandin $F_{1\alpha}$. It was found that the prepared esters and acids *II* with *cis*-configuration do not possess a physiological effect (considering the influence on the formation of hydrochloric acid and pepsine in rats) in contrast to the *trans* isomer *IIIc* in which this effect was observed earlier[7].

EXPERIMENTAL

The infrared spectra were measured on a Perkin-Elmer 325 spectrophotometer, the ^{1}H-NMR spectra on a Varian XL-100-15 (100 MHz) instrument in deuteriochloroform dried over the molecular sieve 4 A, using tetramethylsilane as internal reference, at 37°C. The $Eu(dpm)_3$ used was purchased from Willow Brook Labs. Gas chromatography was carried out on a Varian Aerograph 2100. The solvents were evaporated on a rotatory evaporator under reduced pressure (water pump) and maximum 50°C. For hydrogenation Raney nickel W-2 was used. The final purification of substance *Ic* was carried out on a rotating column of Nester-Faust type NF 136 with an efficiency of 45 theoretical plates. The calculations were carried out on a Tesla 200 computer.

Alkyl ω-(2-Hydroxycyclopentyl)alkanoate *II*

Hydrogen was introduced at 100 atm initial pressure (when Raney nickel was used) or 80 atm (when Adams catalyst was used) to a mixture of 0·1 mol of keto ester *I* in 200 ml of corresponding absolute alcohol (in the case of free keto acid *Ia* hydrogenation was carried out in the same volume of acetic acid) and 1·2 to 1·5 g of Raney nickel or 0·6 g of platinum oxide. The autoclave was heated at 100°C under stirring for 8 hours, and in the case of hydrogenation of keto ester *Ie* at 60–80°C for 6 hours. After filtering off the catalyst and evaporation of the solvent the product was fractionated at reduced pressure. The boiling points, yields, results of elemental analyses and spectral data are summarized in Table I. The results of the ^{1}H-NMR spectra of methyl esters of hydroxy acids *II* are described in Table II. In Tables *IV*–*VI* the spectra are reproduced especially for the complex of hydroxy ester *IIc* with the shift reagent ($Eu(dpm)_3$) together with a similar complex of hydroxy ester *IIIc* (prepared on reduction of the keto compound *Ic* with sodium borohydride[1]). The starting keto ester *Ic* was vacuum distilled on a rotating column and fractions of 99–100% purity of the product (according to GLC), boiling at 152°C/4·5 Torr, were collected.

Isolation of *cis* (*IIc*) and *trans* (*IIIc*) Isomer

The product of hydrogenation of compound *Ic* (3·25 g) was chromatographed on a column of Silica gel CH (Lachema, Brno, 40–100 μ) of 2 × 90 cm dimensions, using first 500 ml of benzene for elution. This was continued with benzene–chloroform while the concentration of chloroform in the mixture was increased after each 500 ml by 10%. The mixture containing 40% of chloroform eluted first the fraction with the *cis* isomer. The elution was carried out at constant pressure (micropump PPM Mikrotechna) and 1 ml/min rate. Fractions of 15 ml volume were collected with an automatic fraction collector. The composition of the fractions was analysed by thin-layer chromatography on silica gel G in ether–chloroform 1 : 4. Detection was carried out with 10% sulfuric acid containing 1% of cerium sulfate and heating, R_F *cis* > R_F *trans* isomer. The isolated amount of the *cis* isomer *IIc* was 1·66 g, while the remaining material was in an inter-

mediate fraction containing a mixture of both isomers, a fraction of 0·25 g of the *trans* isomer, and a first fraction of impurities. In a similar manner 1·07 g of *trans* isomer *IIIc* was obtained from 2·33 g of the product of reduction of substance *Ic* with sodium borohydride[1] after the preceding mixture of both isomers.

Both substances *IIc* and *IIIc* were analysed on a gas chromatograph (length 98 cm, diameter 0·2 cm, stationary phase 5% QF-1 on Chromosorb G, temperature 150°C, FID) before preparative chromatography. The retention times and the percentual composition of both isomers in the product isolated from both types of reduction are given in Table III where the determined mixtures of isomers after reductions of keto esters *Ie* and *If* are also shown. The GLC analysis was also used for a final check of the separated fractions after preparative chromatography of the reduction products of compound *Ic*. Pure isomers *IIc* and *IIIc* were employed for the study of the ^{1}H-NMR spectra of their complexes with $Eu(dpm)_3$ (Table IV–VI), for the computation of their limiting induced shifts (Table VII) and for pharmacological orienting tests.

The elemental analyses were carried out in the Laboratory of Organic Analysis (head Dr L. Helešic) of the Department of Organic Chemistry, the spectra were measured in the Laboratory of NMR Spectroscopy of the same department (head Professor V. Dědek) and in the Laboratory of Absorption Spectroscopy (head Professor B. Hájek), all at the Institute of Chemical Technology, Prague. We thank Mr N. Vodeničar for technical assistance and Mr V. Ineman for gas chromatographic analyses. The computations were carried out in the Computation Centre, Institute of Chemical Technology, Prague, (head Dr V. Říhák).

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