STEREOCHEMICAL STUDIES, XXI*

Studies on Cyclic 2-Hydroxycarboxylic Acids, IV*

Synthesis of *cis*- and *trans*-2-Hydroxycyclooctanecarboxylic Acid. Data on the Reduction of Cyclic Ethyl 2-Ketocarboxylates**

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The preparation of *cis*- and *trans*-2-hydroxycyclooctanecarboxylic acid (**13, 14**) is described. It is shown that *cis*-2-hydroxycyclooctanecarboxylic acid, considered as stereohomogeneous in a recent paper [14], is actually a mixture of the *cis*- and *trans*-isomers. The isomer ratio of the catalytic and sodium borohydride reduction of homologous alicyclic 2-ketocarboxylates (**1—4**) has been studied.

Introduction

In the course of our investigations on the reaction mechanism and conformational analysis of alicyclic 1,3-disubstituted compounds [1—6], it proved necessary to elaborate methods suitable for preparing larger quantities of alicyclic *cis*- and *trans*-2-hydroxycarboxylic acids. We reported earlier [7] on our methods of synthesizing *cis*- and *trans*-2-hydroxycyclopentanecarboxylic acid as well as *cis*- and *trans*-2-hydroxycycloheptanecarboxylic acid.

Stereohomogeneous cyclic 2-hydroxycarboxylic acids can be obtained by reduction of the corresponding 2-ketocarboxylates and subsequent fractionation of the resulting *cis—trans* mixture. However, no suitable methods for the separation of greater quantities of *cis—trans* mixtures were available. The separation of ethyl *cis*- and *trans*-2-hydroxycyclopentanecarboxylates (**5, 6**) was elaborated by PASCUAL and CASTELLS [8], who separated the corresponding dinitrobenzoates by tedious fractional crystallization. Later on MÖHRLE and BAUMANN [9] separated the ethyl *cis*- and *trans*-2-hydroxycyclopentanecarboxylates (**5, 6**) by countercurrent distribution, and recently CAPON and PAGE [10] by preparative gas chromatography.

As we reported [7], a very efficient separation of these compounds, as well as of the corresponding cyclohexane and cycloheptane homologues can be achieved by fractional distillation on a column of about thirty theoretical plates. With this method we succeded in separating the ethyl *cis*- and *trans*-2-hydroxycyclooctanecarboxylate (**11, 12**).

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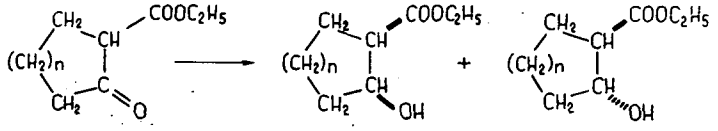
As the efficiency of the distillation depends highly on the isomer ratio of the starting mixture used, it seemed justified to study the isomer ratio of the catalytic and of sodium borohydride reduction.

In the present paper we report on the preparation of *cis*- and *trans*-2-hydroxycyclooctanecarboxylic acid (**13**, **14**) and on our investigations concerning the isomer ratio of the reduction of homologous cyclic ethyl 2-ketocarboxylates.



1 : n = 1 5 : n = 1 6 : n = 1
2 : n = 2 7 : n = 2 8 : n = 2
3 : n = 3 9 : n = 3 10 : n = 3
4 : n = 4 11 : n = 4 12 : n = 4

Fig. 1

Results and discussion

In the reduction of cyclic ethyl 2-ketocarboxylates, the isomer ratio of the reduction products was investigated only in the case of lower homologues [11], though the accuracy of the methods used for determining the isomer ratio, *e.g.* fractional crystallization, or m.p. determination of the 3,5-dinitrobenzoate of the product cannot be considered as sufficient. The reduction of ethyl 2-ketocycloheptanecarboxylate with Adams' PtO_2 catalyst and with sodium borohydride was also performed by PASCUAL *et al.* [12], without giving, however, the isomer ratio.

BHARGAVA, MATUR and SAHARIA, reporting [13] on the synthesis of *cis*- and *trans*-2-hydroxycycloheptanecarboxylic acid, assumed that under the experimental conditions used (sodium borohydride—ethanol, or W-7 Raney nickel catalyst—hydrogen—ethanol), only ethyl *cis*-2-hydroxycycloheptanecarboxylate (**9**) formed, without proving the homogeneity of the product. As we subsequently reported [7], both the catalytic and sodium borohydride reductions, under various experimental conditions, always leads to both isomers, though the *cis* isomer is predominant.

In 1968, SAHARIA and TYAGI supposed [15] the product obtained by sodium borohydride reduction of ethyl 2-ketocyclooctanecarboxylate (**4**) to be stereohomogeneous ethyl *cis*-2-hydroxycyclooctanecarboxylate (**11**).

With respect to the above, it seemed reasonable to study the catalytic and sodium borohydride reductions of the homologous ethyl 2-ketocarboxylates (**1**—**4**) using the less expensive Raney nickel catalyst. As we found earlier [7, 15, 16] that at lower temperatures the reduction of analogous ethyl 2-ketocarboxylates with sodium borohydride yielded a higher *trans* isomer ratio, we studied also the influence of temperature on the reaction under comparable experimental conditions. For determining the *cis*—*trans* isomer ratio we used gas chromatography. Results are summarized in Table I.

It can be seen that the catalytic reduction of all four homologues always yields about 90% *cis* isomer, the same beeing true for the sodium borohydride reduc-

*Table I**

Isomer ratio of the reduction of cyclic ethyl 2-ketocarboxylates (**1**—**4**)

Reaction	Isomer ratio, %					
	$NaBH_4$		Raney nickel/H_2			
	0°C		25°C		60°C	
	cis	*trans*	*cis*	*trans*	*cis*	*trans*
1 → **5**+**6**	31.2	68.8	40.6	60.4	87.3	12.7
2 → **7**+**8**	62.0	38.0	51.7	48.3	88.2	11.8
3 → **9**+**10**	94.1	5.9	91.8	8.2	89.7	10.3
4 → **11**+**12**	92.7	7.3	88.4	11.6	91.2	8.8

Note. * Reaction conditions see: Experimental part.

tion of ethyl 2-ketocycloheptanecarboxylate (**3**) and ethyl 2-ketocyclooctanecarboxylate (**4**), while in the case of the lower homologue the sodium borohydride reduction yields considerably more *trans* isomer than the catalytic process.

13 **14**

Fig. 2

SAHARIA and TYAGI, hydrolysing the product of sodium borohydride reduction of ethyl 2-ketocyclooctanecarboxylate, and assuming it to be homogeneous ethyl *cis*-2-hydroxycyclooctanecarboxylate (**11**), reported a m.p. of 70°C for the *cis*-2-hydroxycyclooctanecarboxylic acid (**13**) [14]. In contrary, by hydrolysis of the gas chromatographically homogeneous ethyl *cis*-2-hydroxycyclooctanecarboxylate, we obtained a m.p. of 97°C for the *cis*-2-hydroxycyclooctanecarboxylic acid (**13**), and 109°C for the *trans* isomer, similarly prepared from gas chromatographically homogeneous ethyl *trans*-2-hydroxycyclooctanecarboxylate (**12**). Stereohomogeneity of the *cis*- and *trans*-2-hydroxycyclooctanecarboxylic acid (**13**, **14**) is unequivocally supported by IR and NMR data (see: Table II and Figs 3 and 4). It follows from the above, that the reduction product of the Indian authors could not be homogeneous, consequently the hydroxy acid they obtained must also have been a mixture of the *cis* and *trans* isomers.

Experimental

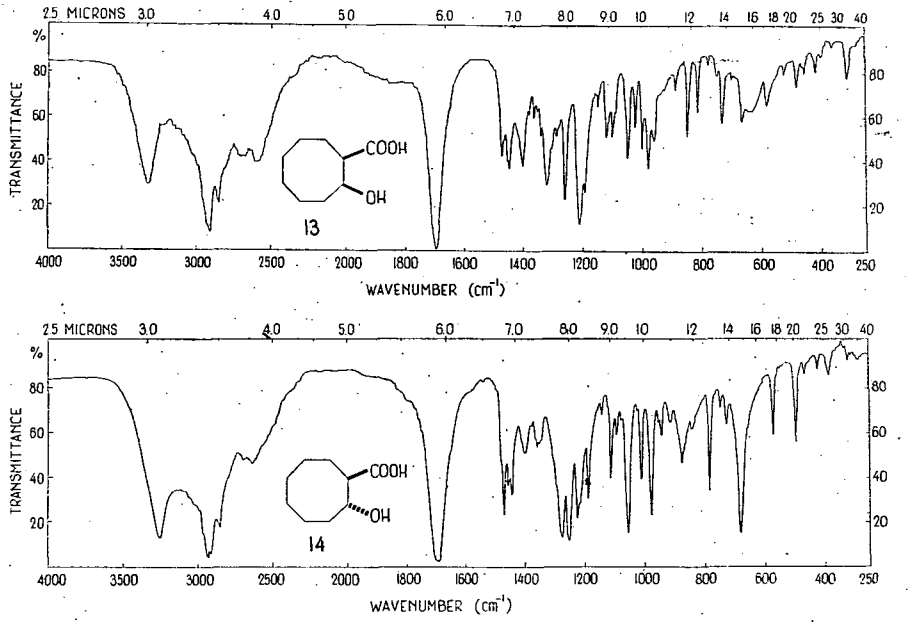
M.ps were determined on a Kofler-block and are uncorrected. IR spectra were obtained in KBr pellets, with a Perkin—Elmer infrared spectrophotometer. NMR measurements were made with a 60 Mc/s J-NM-C-60 (JEOL) spectrometer, $CDCl_3$ was used as solvent and TMS as internal standard.

Table II

IR and NMR data of the cis- and trans-2-hydroxycyclooctanecarboxylic acid (**13, 14**)

Compound	IR data[a]			NMR data[b]		
	νOH (alcohol)	νOH (acid)	νC=O	CH_2 (12)	δ CH(COOH)	δ CH(OH)
13	3320	3500—3200	1698 (sharp)	70—130 Hz	2.75 (12 Hz)	4.25 (10 Hz)
14	3250	3500—2300	1695 (broad)	70—130 Hz	2.65 (20 Hz)	4.10 (20 Hz)

Note. [a] Measurements of IR spectra were made in KBr pellets with a Perkin-Elmer IR spectrophotometer. Spectra see Figs 3 and 4.
[b] Chemical shifts in δ ppm, coupling constants in Hz units. Solvent: $CDCl_3$.



Figs 3 and 4

Reduction of cyclic ethyl 2-ketocarboxylates (**1—4**)

a) The catalytic reductions were performed in abs. ethanol with 0.2 mole ethyl 2-ketocarboxylate using 10.0 g Raney nickel catalyst previously washed with water and ethanol several times, and applying 120 atm starting hydrogen pressure. After the reduction had been completed, the catalyst was filtered off, the solvent removed in vacuum and the isomer ratio of the remaining crude product was deter-

mined by gas chromatography, using a Gazofract 400 C apparatus: column height 2 m; stationary phase: polyethyleneglycol adipate 20%; support: superthermolit 30—40 mesh; temperature 160°C; carrier gas: hydrogen.

b) 200 ml abs. ethanol was placed in a 750 ml three-necked round-bottomed flask equipped with stirrer and reflux condenser, then 0.15 mole sodium borohydride was added in portions under stirring. After the reagent dissolved, 0.1 mole of the corresponding ethyl 2-ketocarboxylate (**1-4**) dissolved in 50 ml abs. ethanol was added dropwise, maintaining the flask at 0°C or 25°C, respectively. The reaction mixture was stirred for 6 hrs, a mixture of 16 ml glacial acetic acid and 150 ml water was added dropwise under stirring. The ethanol was distilled off at reduced pressure (25—30 torr). The remaining mixture separated into two layers and was extracted 4 or 5 times with 100 ml ether and, after drying over Na_2SO_4, the ether was distilled off. The isomer ratio of the remaining cyclic ethyl 2-hydroxycarboxylate was determined as above.

Cis-2-hydroxycyclooctanecarboxylic acid (**13**)

20.0 g (0.10 mole) gas-chromatographically homogeneous ethyl *cis*-2-hydroxycyclooctanecarboxylate (**11**) was shaken with 150 ml 15% NaOH solution at room temperature for 12 hrs. To remove contaminations, the alkaline solution was extracted with 2×100 ml ether and acidified to pH 2 by adding conc. HCl, then extracted with 5×100 ml ether. The combined ethereal solution was dried over Na_2SO_4 and after eveporation gave 12.9 g (74.8%) *cis*-2-hydroxycyclooctanecarboxylic acid (**13**), which was crystallized from benzene, m.p. 95—96°C. After three recrystallizations from benzene the m.p. was 97°C, which remained constant on further recrystallization (Lit. [14] m.p.: 70°C). IR spectrum: Fig. 3, NMR spectrum: Table II.

$C_9H_{16}O_3$ (172.23). Calcd. C 62.77; H 9.36. Found C 62.50; H 8.96%.

Trans-2-hydroxycyclooctanecarboxylic acid (**14**)

2.0 g (0.01 mole gas-chromatographically homogeneous ethyl *trans*-2-hydroxycyclooctanecarboxylate (**12**) was hydrolysed as above to yield 1.55 g (89.9%) *trans*-2-hydroxycyclooctanecarboxylic acid (**14**). This was crystallized from benzene, m.p. 105—106°C, recrystallized two times from benzene and three times from ether. M.p. 109°C, which remained constant on further recrystallization. IR spectrum: Fig. 4, NMR spectrum: Table II.

$C_9H_{16}O_3$ (172.23). Calcd. C 62.77; H 9.36. Found C 62.79; H 9.59%.

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СТЕРЕОХИМИЧЕСКИЕ ИССЛЕДОВАНИЯ, XXI ИЗУЧЕНИЕ ЦИКЛИЧЕСКИХ 2-ОКСИКАРБОНОВЫХ КИСЛОТ, IV СИНТЕЗ *ЦИС*- И *ТРАНС*-2-ОКСИЦИКЛООКТАНОВОЙ КИСЛОТЫ. ДАННЫЕ О ВОССТАНОВЛЕНИИ ЦИКЛИЧЕСКИХ СЛОЖНЫХ ЭФИРОВ 2-КЕТОКАРБОНОВОЙ КИСЛОТЫ

Г. Бернат, Дь. Гёндёш, Л. Гера

Описан синтез *цис*- и *транс*-2-оксициклооктановой (**13, 14**) кислоты. Показано, что описанная недавно в работе [14] *цис*-2-оксициклооктановая кислота является смесью *цис*- и *транс*-изомеров. Изучено распределение изомеров гомологического ряда сложных эфиров алициклической 2-кетокарбоновой кислоты (**1—4**) при каталитическом и натрий-боргидридном восстановлении.