Tetrahedron. Vol. 23, pp 4331 to 4336 Pergamon Press Ltd. 1967. Printed in Great Britain

THE CONFIGURATIONS AND CONFORMATIONS OF 2-CARBOXYCYCLOPENTANOLS AND THE CORRESPONDING METHYL AND ETHYL ESTERS

H. BAUMANN, N. C. FRANKLIN[1] and H. MÖHRLE[2]

Pharmazeutisch-Chemisches Institut der Universitat Tübingen, Germany

(*Received* 10 *February* 1967; *accepted for publication* 10 *March* 1967)

Abstract—The NMR spectra of *cis*- and *trans*-2-carboxycyclopentanol and the corresponding methyl and ethyl esters have been measured, and from the chemical shift of the proton adjacent to the OH group and the band width of this signal, it has been possible to assign the configurations of these pairs of isomers. It was observed that the difference in chemical shift for this proton in the two isomers was considerably smaller than that found in the corresponding cyclohexane derivatives, a pair of which have also been measured. Thus only when the compounds are extremely pure is it possible to assign the configurations in this way.

IN CONNECTION with the investigations into the reactions of a series of lactams being carried out in this Institute,[3] it was necessary to develop a method of rapidly assigning the stereochemistry to the 2-carboxycyclopentanols and some of their esters. In view of the success in applying the techniques of NMR spectroscopy to assign the configuration and conformations of various cyclohexanols,[4] it was decided to investigate this method. The compounds were of the general formula as shown in Fig. 1, and Table 1 sets out the full list of investigated compounds.

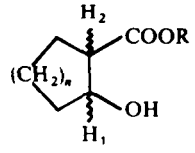

FIG. 1. General formula.

The carboxy-derivatives were prepared from the ethyl ester of the 2-carboxycyclanone, which was reduced with platinum oxide to the corresponding cyclanol, the isomeric mixture of which was separated either by counter-current distribution or by re-crystallization of selected derivatives. (Experimental Section).

It has been recently shown that four criteria can be used in determining the stereochemistry of such pairs of isomers.[5] The first of these, the area under the signals can be used to determine the percentage composition of an isomeric mixture, but only if signals can be observed which can be definitely assigned to each individual isomer.

[1] Present address: Lilly Research Laboratories Limited, Bromborough Park, New Ferry, Wirral, Cheshire, England.

[2] To whom all inquiries should be addressed.

[3] H. Möhrle and H. Baumann, *Arch. Pharmaz.* **299**, 355 (1966), and previous papers in this series.

[4] H. Feltkamp and N. C. Franklin, *Tetrahedron* **21**, 1541 (1965).

[5] H. Feltkamp and N. C. Franklin, *Angew. Chem.* **77**, 798 (1965); *Internat. Edit.* **4**, 774 (1965).

TABLE 1. SUMMARY OF THE INVESTIGATED COMPOUNDS.

Compound	Configuration	R	Ring size, n =	Name of ring
I	*cis*	H	1	cyclopentyl
II	*trans*	H	1	cyclopentyl
III	*cis*	CH_3	1	cyclopentyl
IV	*trans*	CH_3	1	cyclopentyl
V	*cis*	CH_2CH_3	1	cyclopentyl
VI	*trans*	CH_2CH_3	1	cyclopentyl
VII	*cis*	H	2	cyclohexyl
VIII	*trans*	H	2	cyclohexyl
IX	*cis*	CH_3	2	cyclohexyl
X	*trans*	CH_3	2	cyclohexyl

The NMR spectrum of the mixture of the *cis*- and *trans*-2-carboxycyclopentanol (I and II) showed that all the possible peaks which might have been used, (peak due to H_1, peak due to H_2, peak due to OH protons, etc) appeared at the same field, so that neither the area under the signal, nor any of the remaining criteria could be used to determine the composition of the isomeric mixture.

Examination of the NMR spectra of the separated isomers showed however that the configurations could be assigned on the basis of the NMR results. These are set out in Table 2.

TABLE 2. SUMMARY OF THE NMR DATA FOR THE CYCLOPENTYL COMPOUNDS

Compound	Configuration	H_1		H_2	
		Chemical shift	Bandwidth (in c/s)	Chemical shift	Bandwidth (in c/s)
I	*cis*	5·50 τ	11·0	7·23 τ	23·0
II	*trans*	5·59 τ	18·0	7·25 τ	25·0
III	*cis*	5·55 τ	11·0	7·28 τ	23·0
IV	*trans*	5·61 τ	17·5	7·30 τ	25·0
V	*cis*	5·60 τ	11·0	7·31 τ	22·0
VI	*trans*	5·63 τ	17·5	7·40 τ	25·0

Turning to the remaining criteria which can be used to determine the stereochemistry of such isomeric pairs it is seen that the chemical shift can be used as a basis to assign the configurations. In the *cis* isomers the chemical shift of the H_1 proton is at lower field than in the *trans* isomers, although the difference of 0·03 τ to 0·09 τ is very much smaller than that found in the corresponding cyclohexane derivatives (VII and VIII). A similar difference in chemical shift is observed for the C_2 proton.

However, considerably more interesting is the difference in the band width of the C_1 and C_2 protons in each isomeric pair. In all the *cis* isomers (I, III and V) the band width, measured between the first and last lines of the multiplet, of the signal due

to the C_1 proton is always about 11 c/s. In the *trans* isomers though, this band width is always 18 c/s. This difference is due to the different environment of this proton in the *cis* and *trans* isomers and the difference will be discussed more fully later. Another interesting feature is that there is a considerable difference in the band width of the signal due to the proton on C_1 and the proton on C_2 in any given isomer. If the cyclopentanols existed in a planar ring form it would be expected that the band width of the signal due to the C_1 and C_2 protons would be the same, when the influence of the different electronegativities of the substituents on the coupling constants, and hence the band widths, is neglected.[6] This is, however, not the case,

FIG. 2. Envelope conformation of the cyclopentyl ring.

and thus it is highly probable that in both isomers the cyclopentane ring exists in either the "puckered" or in the "envelope" form[7] (Fig. 2). It has, however, been pointed out[8] that in substituted cyclopentanes the "envelope" form is probably more stable, and corresponds to a definite energy minima. In the case of the *trans* isomers, if the ring does exist in the "envelope" form, the form with the two substituents in the quasi-equatorial position (Fig. 3A) will obviously be more stable than other conceivable forms (e.g. Fig. 3B) due to the decrease in the non-bonding interactions. The question of which of the two substituents will be found on the "flap" of the envelope can be resolved by considering their relative size, for the larger of these will occupy the least sterically hindered position. Although it is not possible to take the ΔG values of the two substituents as measured in the cyclohexane ring system as an absolute criterion (primarily because the *syn-anti* non-bonded interactions[9] between the quasi-axial substituent and the quasi-axial proton on the carbon atom two bonds away are not the same in cyclohexyl and cyclopentyl systems),

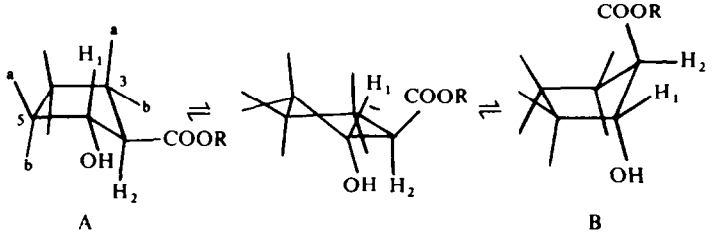

FIG. 3. The most stable conformations of *trans*-2-carboxycyclopentanol

[6] [a] K. L. Williamson, *J. Am. Chem. Soc.* **85**, 2709 (1963). [b] P. Lazlo and P. von R. Schleyer, *Ibid.* **85**, 2709 (1963).

[7] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 200. Interscience, New York (1965).

[8] F. V. Brutcher, T. Roberts, S. J. Barr and N. Pearson, *J. Am. Chem. Soc.* **81**, 4915 (1959).

[9] E. L. Eliel, *Angew. Chem.* **77**, 784 (1965); *Internat. Edit.* **4**, 761 (1965).

it is possible to assume that the order of magnitude will be similar. Hence the larger of the two groups will take up the less hindered position, i.e. on the "flap" of the envelope.

Thus the carboxy group will take up this position, and here it will have a cyclohexane type of neighbourhood; it is thus to be expected that the band width of the adjacent proton (H_2) will be almost the same as that found in a similar substituted cyclohexane. This has been confirmed by measuring the NMR spectra of *cis*- and *trans*-2-carboxycyclohexanol, the results of which are set out in Table 3. The proton

TABLE 3. SUMMARY OF THE NMR DATA FOR THE CYCLOHEXYL COMPOUNDS.

Compound	Configuration	H_1				H_2			
		Chemical shift	Bandwidth (in c/s)	J_{aa} (in c/s)	J_{ae}	Chemical shift	Bandwidth (in c/s)	J_{aa} (in c/s)	J_{ae}
VII	*cis*	5·73 τ	8·5	—	—	7·46 τ	17·5	7·5*	3·0*
VIII	*trans*	6·29 τ	25·0	10·2	4·5	7·72 τ	25·2	10·7	3·5
IX	*cis*	5·85 τ	11·0	—	—	7·50 τ	16·5	7·0*	2·5*
X	*trans*	6·25 τ	25·0	—	4·5	7·72 τ	25·0	10·5	4·0

* = Time averaged coupling constants.

on C_1, adjacent to the hydroxy group will then have as neighbouring protons that on C_2, with a vicinal angle of about 180°, and the two protons on C_5. These will have an approximate vicinal angle of 0–20° and 110–130°. It is therefore to be expected that the sum of the coupling constants J_{5a}^{1} plus J_{5b}^{1} will be smaller than the sum of J_{3a}^{2} plus J_{3b}^{2}, leading to a smaller band width for proton on C_1. It is not possible to express this quantitatively as the influencing factors are not well enough known, it is, however, certain that the most stable conformation of the *trans* compounds (II, IV and VI) is that shown in Fig. 3A.

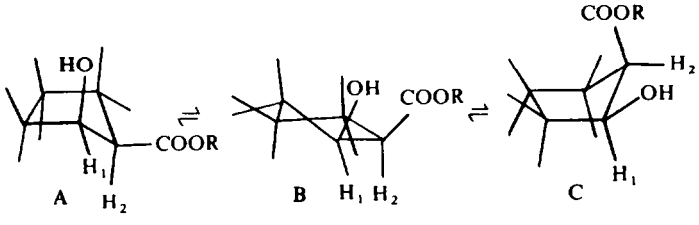

FIG. 4. The most stable conformations of *cis*-2-carboxycyclopentanol.

In the case of the *cis* isomers, it is not so likely that any one conformation will be preferred, for if the cyclopentane ring exists in the "envelope" form, one of the substituents will have to be in the quasi-axial position (Fig. 4A or 4C), and the energy of these forms will be higher than the most stable "envelope" form (Fig. 3A) of the *trans* compounds. However, the band width of the signals due to the C_1 and C_2 protons are considerably different (11 c/s and 23 c/s respectively). Although these could be average band widths, due conformational change of the type 4A ⇌ 4B ⇌ 4C

it seems that the position of equilibria must lie in the direction of the largest substituent (COOH) being in the quasi-equatorial position, and hence the adjacent proton quasi-axial with the vicinal angles between this C_1 proton and its neighbours being either very small or very large resulting in large coupling constants. It has been shown that the analysis of the band width can give useful information about the equilibrium position in substituted cyclohexanes[4] but it has been pointed out that for this method to be used with any degree of accuracy it is necessary to know the band widths which correspond to the extreme conformations, and this information can often be taken from model compounds. Unfortunately no such model compounds were available, nor is it to be expected that if the equilibration rate between the conformers, 4A $\rightleftharpoons$ 4B $\rightleftharpoons$ 4C is slowed down so that at low temperature the NMR spectrum can be measured, there will be sufficient separation of any of the peaks to carry out an analysis in this way. Hence no quantitative measure of the equilibrium can be attempted.

As mentioned, the NMR spectra of the *cis*- and *trans*-2-carboxy-cyclohexanols (VII and VIII) have also been measured, and from Table 2 it was possible to assign the configurations by simple examination for not only did the proton on C_1 appear at considerably lower field in the *cis* isomer, (0·56 τ lower in the *cis* isomer) but also the band width of 25 c/s in the *trans* isomer for the C_1 proton confirms the expected axial orientation of this proton in conformer 6A. The *cis* isomer can exist in either conformer 5A or 5B of which 5A will be preferred on theoretical grounds.

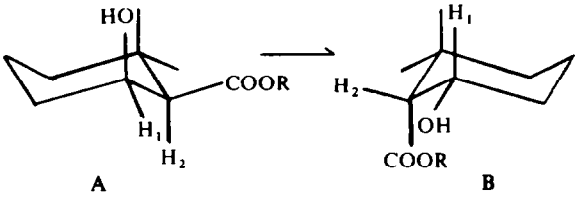

FIG 5. The most stable conformations of *cis*-2-carboxycyclohexanol.

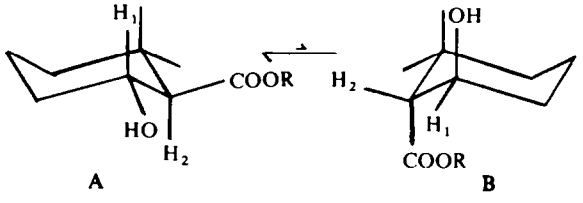

FIG. 6. The most stable conformations of *trans*-2-carboxycyclohexanol.

As the necessary model compounds were not available, nor was it possible to obtain the spectrum of the *cis* isomer at low temperature, it was not possible to use the area under the peaks, the difference in chemical shift or the band width methods of conformational analysis. However, the fourth method of analysis based on the average coupling constants[10] could be applied. Using equation 1, the mole

[10] [a] F. A. L. Anet. *J. Am Chem. Soc.* **84**, 1503 (1962); [b] H. Booth. *Tetrahedron* **20**, 2211 (1964).

fraction x of conformer 5A could be determined, although J_{ee} had to be taken from cyclohexanol itself.[10a]

$$J_{aa}^{ee} = x J_{aa} + (1 - x) J_{ee} \quad (1)$$

The accuracy of the method was not very good, as it gave a value of $x = 0{\cdot}6$, whilst from consideration of the ΔG values[9] it was to be expected that the value of x would be 0·75 to 0·8. However, it confirmed that the most stable conformer was in fact 5A, with the carboxy group in the predominantly equatorial position.

It has thus been shown that it is possible to use NMR spectroscopy in the configurational analysis of cyclopentane derivatives, but because the geometry of the cyclopentane ring is not fully understood, and varies much more with the substituents than the cyclohexane ring it is considerably more difficult to carry out an accurate conformational analysis of such ring systems.

EXPERIMENTAL

The NMR spectra were determined at 27° as approximately 10% solns in $CDCl_3$ at either 60 Mc/s (Varian A60A) or at 100 Mc/s (Varian HA 100).

Preparation. 2-Carboxycyclanone ethyl ester was reduced in EtOH with PtO_2 (Adams catalyst) to give an isomeric mixture of *cis*- and *trans*-2-carboxycyclanol.

Separation of the isomeric mixtures

(a) The isomers could be separated by a Craig counter-current distribution technique, the exact conditions of which will be published later in a full paper.[11]

(b) *cis*- and *trans*-*2-Carboxycyclopentanol*[12] The 3,5-dinitrobenzoates of the isomeric mixture of the ethyl esters of carboxycyclopentanol were separated through fractional crystallization. The *cis* had a m.p. of 116–117° (Lit.[12] 116–116·8°), and the *trans* isomer a m.p. of 75·5° (Lit.[12] 76·2–77·1°).

Acknowledgements—The authors wish to thank the Deutsche Forschungsgemeinschaft for financial support for this work.

[11] H. Möhrle and H. Baumann, Results to be published.

[12] J. Pascual and J. Castells, *J. Am. Chem. Soc.* **74**, 2899 (1952).