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Cyclic Hydroxycarboxylic Acids. II* Lactonization Reactions on 2-Hydroxycyclopentanecarboxylic Acids and 3-Hydroxyprolines

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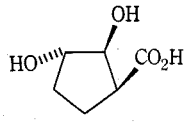
Abstract

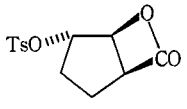
The racemates of *cis*-2-hydroxycyclopentanecarboxylic acid and of *cis*-3-hydroxy-*N*-tosylproline yield corresponding *β*-lactones upon treatment with cold tosyl chloride–pyridine. Similar treatment of *trans*-2-hydroxycyclopentanecarboxylic acid gives cyclopent-1-enecarboxylic acid, but *trans*-3-hydroxy-*N*-tosylproline is unchanged. Unlike in other 3-hydroxyprolines, the proline protons in the *N*-tosyl *β*-lactone have a completely first-order p.m.r. spectrum which is analysed.

Introduction

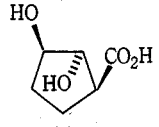
In Part I we prepared the hitherto unknown 2,3-dihydroxycyclopentane-1-carboxylic acids (1) and (3).[1] In the course of establishing their relative stereochemistry we discovered that overnight treatment of each with tosyl chloride (1·5 molar equiv. per hydroxyl group) in pyridine at 0° gave the *β*-lactone (2) (41% after recrystallization) and the *γ*-lactone (4) (40% after recrystallization) respectively. This was the first example of direct dehydration of a *β*-hydroxy acid to a *β*-lactone by tosyl chloride–pyridine, and we have sought other examples. The consequences of treating the *cis*- and *trans*-isomers of 2-hydroxycyclopentanecarboxylic acid† and of 3-hydroxy-*N*-tosylproline† with tosyl chloride–pyridine are reported here.



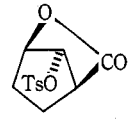
(1)
m.p. 105°



(2)
m.p. 89°



(3)
gum



(4)
m.p. 91°

2-Hydroxycyclopentane-1-carboxylic Acid Series

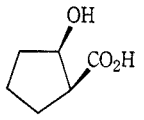
The known *cis*- and *trans*-*β*-hydroxy acids (5) and (7) were prepared and left overnight with tosyl chloride (1·15 molar equiv.) in cold pyridine.

The *cis*-hydroxy acid (5) gave as the major product (39% after preparative t.l.c.) the oily *β*-lactone (6) whose composition was obtained by high resolution mass spectro-

* Part I, *Aust. J. Chem.*, 1976, **29**, 1493.
† Racemates are intended throughout.

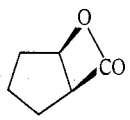
[1] Philp, R. P., and Robertson, A. V., *Aust. J. Chem.*, 1976, **29**, 1493.

metry. Its carbonyl absorption was at ν_{max} 1824 (liquid film), well within the range for β-lactones;[1] the 3-tosyloxy analogue (2) has ν_{max} 1841 ($CHCl_3$).[1] This result demonstrates that the unprecedented β-lactonization process (1) → (2) has some generality, and is confirmatory evidence for the stereochemistry allotted in the dihydroxy acid series (1) and (3).



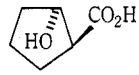
(5)

m.p. 53°



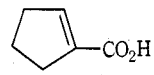
(6)

oil



(7)

m.p. 69°



(8)

m.p. 119°

In the p.m.r. spectrum of the 1,2,3-trisubstituted cyclopentane (2), the signals from H 1, H 2, and H 3 were isolated and it was straightforward to extract the relevant coupling constants $J_{1,2}$ 3·7 Hz and $J_{2,3}$ *c.* 0 Hz.[1] By contrast, the p.m.r. signals from the disubstituted cyclopentane (6) are less dispersed and more split. However, the multiplet from H 2 was essentially a 1 : 2 : 1 triplet, showing couplings of *c.* 3·5 Hz from two adjacent nuclei, although there are three vicinal hydrogens. An interpretation which matches well with the couplings in the 3-substituted analogue (2) would be $J_{1,2}$ *c.* 3·5, $J_{2,3\text{-}trans}$ *c.* 0, and $J_{2,3\text{-}cis}$ *c.* 3·5 Hz.

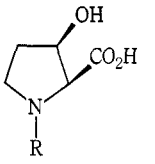
Similar treatment of the *trans*-hydroxy acid (7) with tosyl chloride–pyridine gave as the main product (53%) the known α,β-unsaturated acid cyclopent-1-enecarboxylic acid (8). Its structure was confirmed by comparison with authentic material. This compound would be formed by tosylation of the hydroxyl group followed by β-elimination of tosic acid. An analogous β-elimination from γ-lactone (4) is prohibited by Bredt's rule. Put another way, the fact that (4) was produced proves that lactonization through a mixed anhydride mechanism is faster than tosylation of the 2-hydroxyl. Had the rates been reversed, elimination to a 3-substituted cyclopent-1-enecarboxylic acid should have occurred, in which event it is sterically impossible for the carboxyl to lactonize.

3-Hydroxyproline Series

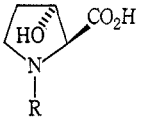
Racemic *cis*- and *trans*-3-hydroxyprolines were prepared after some trouble by several modifications of the method of Sheehan and Whitney.[2] The point at which they claimed to have separated diastereomers was fractional crystallization of 2-bromo-3-methoxy-5-phthalimidopentanoic acid isomers. They found their fraction 'IIa' led to pure *cis*-3-methoxyproline (24%). Their other fraction, presumed to be the second diastereomer 'IIb', led to a mixture of *cis*- (21%) and *trans*-3-methoxyprolines (17%). They did not try to account for this result, but an explanation became apparent in the present work. P.m.r. spectra provide a good assay for the two diastereomers; their methoxyl singlets differ in chemical shift, and so do the H 2 doublets ($J_{2,3}$ 6·5 Hz). In our laboratory the first fraction above was substantially pure 'IIa' (*c.* 95%) but the second was still a mixture of 'IIa' and 'IIb' (5 : 4). We therefore found it more satisfactory not to attempt to separate the bromomethoxyphthalimidopentanoic acids, but to fractionally crystallize the copper salts of the *cis*- and *trans*-3-methoxyprolines, following another separation process described by Sheehan and Whitney.[2] De-

[2] Sheehan, J. C., and Whitney, J. G., *J. Am. Chem. Soc.*, 1963, **85**, 3863.

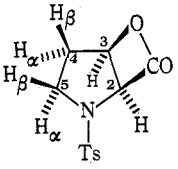
methylation gave the free amino acids (9) and (11) which were converted into their known *N*-tosyl derivatives (10) and (12) by standard methods.[3–5]



(9) R = H
(10) R = Ts



(11) R = H
(12) R = Ts



(13)
m.p. 114°

When *cis*-3-hydroxy-*N*-tosylproline (10) was left overnight with tosyl chloride (2 molar equiv. were used) in cold pyridine, the crystalline *β*-lactone (13) formed almost quantitatively. Its carbonyl frequency was at ν_{max} 1847 cm^{-1} ($CHCl_3$), and its p.m.r. spectrum is analysed in detail below.

Tosyl chloride–pyridine therefore has definite synthetic utility for cyclizing *β*-hydroxy acids directly to their *β*-lactones. So far there has been no general method to accomplish this process, and the difficulties and the few indirect synthetic approaches to *β*-lactones were summarized in Part I.[1] We are investigating whether tosyl chloride–pyridine will also be effective with acyclic and other *β*-hydroxy acids, or whether there is something unique about our examples (2), (6) and (13) in which the four-membered lactone is fused to a five-membered ring.* In these cases *β*-lactonization proceeds just as well as *γ*-lactonization from similar *γ*-hydroxy acids, e.g. (3) → (4): the preferred reagent for generating the *γ*-lactone from an *N*-protected *cis*-4-hydroxyproline is tosyl chloride–pyridine.[6]

By contrast, *trans*-3-hydroxy-*N*-tosylproline (12) was unchanged after similar exposure to tosyl chloride–pyridine. Its secondary hydroxyl group must be unusually inert to *O*-tosylation. This stability would not seem to reside in the geometry imposed by the five-membered ring, to judge from the relatively normal reactivity of the carbocyclic counterpart (7) which must *O*-tosylate satisfactorily before *β*-elimination yields conjugated acid (8). Similarly, the *trans*-2-hydroxyl group in (3) did tosylate satisfactorily to produce the observed product (4).

Part III of this series is devoted to a comparative study of tosylation rates.[5] It emerges that *O*-tosylation by tosyl chloride–pyridine of both *cis*- and *trans*-3-hydroxy-*N*-tosylproline methyl esters is extremely slow, although acetylation in acetic anhydride –pyridine proceeds at ordinary rates. In the case of the *cis*-hydroxy acid (10), for-

* *Note added in proof.*—Independently of our work (first reported by Philp, R. P., Ph.D. Thesis, University of Sydney, 1972), successful conversion of some *β*-hydroxy acids into *β*-lactones with cold benzenesulphonyl chloride–pyridine has been achieved (Adam, W., Baeza, J., and Liu, J.-C., *J. Am. Chem. Soc.*, 1972, **94**, 2000; Krapcho, A. P., and Jahngen, E. G. E., *J. Org. Chem.*, 1974, **39**, 1322, 1650). Their successful examples were heavily substituted, and lactones were not isolated from the least substituted cases (*β*,*β*-disubstituted *β*-hydroxy acids). Their interest was a general synthesis of highly substituted olefins from *β*-hydroxy acids by thermolysis of the intermediate *β*-lactones, and for this overall purpose a more direct dehydration process has been announced (Hara, S., Taguchi, H., Yamamoto, H., and Nozaki, H., *Tetrahedron Lett.*, 1975, 1545).

[3] Blake, J., Willson, C. D., and Rapoport, H., *J. Am. Chem. Soc.*, 1964, **86**, 5293.
[4] Irreverre, F., Morita, K., Robertson, A. V., and Witkop, B., *J. Am. Chem. Soc.*, 1963, **85**, 2824.
[5] Philp, R. P., and Robertson, A. V., *Aust. J. Chem.*, 1977, **30**, 131.
[6] Patchett, A. A., and Witkop, B., *J. Am. Chem. Soc.*, 1957, **79**, 185.

mation of the *N,O*-ditosyl acid does not compete significantly against the mixed anhydride mechanism leading to the *β*-lactone (13).

P.M.R. Analysis for 3-Hydroxyproline β-Lactone (13)

Compounds in the 3-hydroxyproline series have complicated p.m.r. spectra. The spectra are even more complex than in the 4-hydroxyproline series[7–10] since the pair of pyrrolidine methylene groups are adjacent in the 3-hydroxy compounds. Each of the protons on C4 and C5 has a separate chemical shift, which generates an ABXY pattern, with H4*α* and H4*β* being further coupled to H3. Full analysis is therefore a specialist project, and does not appear to have been undertaken for any member of the 3-hydroxyproline series yet. The spectra are of course valuable for confirming purity and constitution, but the only coupling constant that can be extracted straightforwardly is $J_{2,3}$[3,4,5,11] from the H2 doublet.

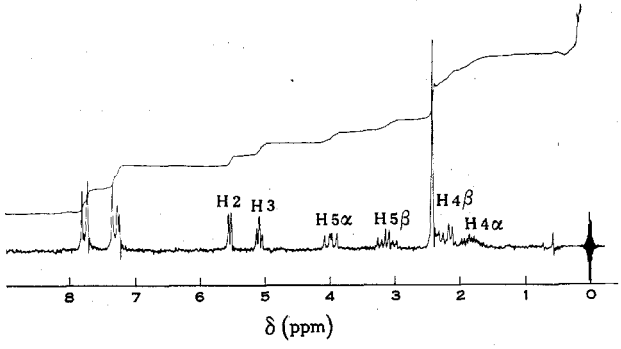


Fig. 1. 100-MHz spectrum of *β*-lactone (13) in $CDCl_3$.

The *β*-lactone (13) proves to be an exception. Its p.m.r. spectrum is shown in Fig. 1. The *N*-tosyl signals are at *δ* 2·42 (Me), 7·34 and 7·80 (ArH). Complete analysis of the proline ring signals by first-order methods was possible and the results are listed in Table 1.

Table 1. First-order p.m.r. parameters for proline protons of β-lactone (13)

Chemical shifts (*δ*)		Coupling constants (Hz)			
H2	5·56	$J_{2,3}$ (*cis*)	4·1	$J_{4\alpha,5\beta}$ (*trans*)	11·4
H3	5·11	$J_{3,4\alpha}$ (*cis*)	4·3	$J_{4\beta,5\alpha}$ (*trans*)	*c.* 0
H4*α*	1·80	$J_{3,4\beta}$ (*trans*)	*c.* 0	$J_{4\beta,5\beta}$ (*cis*)	5·8
H4*β*	2·23	$J_{4\alpha,4\beta}$ (*gem*)	14·6	$J_{5\alpha,5\beta}$ (*gem*)	11·2
H5*α*	4·01	$J_{4\alpha,5\alpha}$ (*cis*)	8·2		
H5*β*	3·13				

The chemical shifts for H2 and H3 were assigned on the basis of their relative multiplicities and were confirmed by spin-decoupling experiments. The H3 multiplet is only a triplet, although there are three vicinal protons: two of the couplings are virtually identical and the third is zero. The two H5 signals are the doublet of doublets

[7] Andreatta, R. H., Nair, V., and Robertson, A. V., *Aust. J. Chem.*, 1967, **20**, 2701.
[8] Abraham, R. J., and McLauchlan, K. A., *Mol. Phys.*, 1962, **5**, 195, 513.
[9] Abraham, R. J., and Thomas, W. A., *J. Chem. Soc.*, 1964, 3739.
[10] Pogliani, L., and Ellenberger, M., *Spectrosc. Lett.*, 1973, **6**, 261.
[11] Wolff, J. S., Ogle, J. D., and Logan, M. A., *J. Biol. Chem.*, 1966, **241**, 1300.

at δ 4·01 and the doublet of triplets at 3·13. The assignment of these between H 5α and H 5β depends on a conformational argument below. To produce their unexpectedly simple splitting patterns, however, one of the four vicinal couplings $J_{4,5}$ must be zero, and another must coincidentally approximate the geminal coupling $J_{5\alpha,5\beta}$. Although it may not be clearly evident from Fig. 1, expanded traces reveal the two H 4 signals as a doublet of doublets at δ 2·23, and a 16-line pattern at 1·80 which is a simple doublet of doublet of doublet of doublets. The multiplicity of the 2·23 resonance is due to the geminal coupling $J_{4\alpha,4\beta}$ and one vicinal coupling (a $J_{4,5}$); the other two vicinal couplings that might have been expected are the zero ones noted above (a $J_{3,4}$ and the other $J_{4,5}$). Detailed measurements of all the line separations yielded the observable couplings listed in Table 1 (each of the four couplings contributing to the δ 1·80 hexadecaplet can be measured eight times in that multiplet alone!).

We assign the δ 2·23 signal to H 4β and the 1·80 signal to H 4α by using two arguments of analogy that reinforce each other. Firstly, in numerous analyses of spectra of 4-substituted[7] and 3,4-disubstituted prolines,[12] we find that for a *cis*/*trans* pair of vicinal coupling constants where one is of medium magnitude and the other is very small or even zero, the general principle of the Karplus rule still applies: the *cis* protons (more or less eclipsed) are associated with the larger coupling. The 4·3 Hz coupling to H 3 is therefore the *cis* $J_{3,4\alpha}$, and the zero coupling is the *trans* $J_{3,4\beta}$. Secondly, the equivalent couplings cited above for the carbocyclic β-lactones (2) and (6) yield the same assignment (they also have a zero *trans* coupling).

There remains the problem of assigning the two H 5 signals to H 5α and H 5β. Although their chemical shift difference is 0·88 ppm, our experience is that it is not yet possible to assign such chemical shifts by predicting the relative shielding and deshielding from the functional groups across the ring and on the nitrogen. Karplus considerations are therefore invoked again, and any interpretation hinges on explaining the fact that of the four vicinal 4,5 couplings, one is zero and the other is abnormally large, viz. 11·4 Hz. The latter value is far larger than any of the 4,5 vicinal couplings previously observed for *cis*- and *trans*-4-substituted prolines.[7,9] It is also significantly larger than any of these couplings in proline (free amino acid in D_2O at pH 11·7) which are as follows: $J_{4\alpha,5\alpha}$ 8·0, $J_{4\alpha,5\beta}$ 5·5, $J_{4\beta,5\alpha}$ 5·7, $J_{4\beta,5\beta}$ 7·7 Hz.[13] We conclude that the protons coupled by 11·4 Hz are a *trans* pair in an antiperiplanar conformation. Since the coupling is from H 4α, its partner in the large coupling must then be H 5β; assignment of the δ 3·13 signal to H 5β and the 4·01 signal to H 5α follows.

Examination of a Dreiding model reveals only one conformation that satisfies all these assignments. The model is fairly rigid except for C 5 which is able to move about 40° above or below the plane formed by N, C 2, C 3, and C 4. When the five-membered ring is fully puckered with C 5 on the same side of the ring as the lactone, the dihedral angle between H 4α and H 5β approaches 180°, that between H 4β and H 5α is *c.* 90°, and that between H 3 and H 4β is *c.* 90°. The Karplus requirements for the very large coupling $J_{4\alpha,5\beta}$ and the two zero couplings $J_{4\beta,5\alpha}$ and $J_{3,4\beta}$ are simultaneously satisfied.

The geminal coupling constants fit well for their environment, both in terms of theoretical prediction[14] and empirical analogy.[15] No sign determinations have been made but both J_{gem} are presumably negative. The value of $J_{4\alpha,4\beta}$ (−14·6 Hz) is

[12] Hudson, C. B., Robertson, A. V., and Simpson, W. R. J., *Aust. J. Chem.*, 1975, **28**, 2479.
[13] Ellenberger, M., Pogliani, L., Haüser, K., and Valat, J., *Chem. Phys. Lett.*, 1974, **27**, 419.
[14] Bothner-By, A. A., *Adv. Magn. Reson.*, 1965, **1**, 195.
[15] Cookson, R. C., Crabb, T. A., Frankel, J. J., and Hudec, J., *Tetrahedron*, 1966, Suppl. No. 7, 355.

similar to $J_{3\alpha,3\beta}$ in *cis*- and *trans*-4-hydroxyprolines,[7,9] and more negative than $J_{4\alpha,4\beta}$ (−11·0 Hz) in the proline anion[13] as expected for the effect of an electronegative 3-substituent. The value of $J_{5\alpha,5\beta}$ (−11·2 Hz) is typical for *N*-tosylprolines.[7]

The value of $J_{2,3}$ (4·1 Hz) compares well with the vicinal coupling at the *cis* ring-fusion in the carbocylic lactones (2) and (6) (3·7[1] and *c.* 3·5 Hz respectively). As was noted in Part I,[1] the *β*-lactones typify the general rule that vicinal coupling constants in caged structures are much smaller than their ring-opened counterparts. For example *cis*-3-acetoxy-*N*-tosylproline methyl ester has $J_{2,3}$ 7·1 Hz;[5] 2,3-*cis*-3,4-*trans*-3,4-diacetoxy-*N*-tosylproline methyl ester has $J_{2,3}$ 6·4 Hz;[12] and 2,3-*cis*-3,4-*cis*-3,4-ditosyloxy-*N*-tosylproline t-butyl ester has $J_{2,3}$ 7·2 Hz.[16]

β-Lactone (13) is the first 3-hydroxyproline derivative in which the H 2 doublet is clearly downfield from the H 3 signal (see Fig. 1). For example, for the free amino acids in D_2O, the H 3 multiplet is downfield by 0·57 ppm in the *cis*-stereoisomer, and by 0·60 ppm in the *trans*-stereoisomer;[11] *N*-tosylation shifts the H 2 signal so that it overlaps the H 3 multiplet (*cis*-3-hydroxy-*N*-tosylproline and its methyl ester[5]); and then esterification of the 3-hydroxyl shifts H 3 downfield again—in *cis*-3-acetoxy-*N*-tosylproline methyl ester, the chemical shifts ($CDCl_3$) are *δ* 4·57 (H 2) and 5·28 (H 3).[5] Reversal of these normal trends in the *β*-lactone (13) implies specific deshielding. Comparing the free *β*-hydroxy acids (1), (5) and (10) with their *β*-lactones (2), (6) and (13) for the effect of lactonization on the chemical shifts of the relevant protons (H 1 and H 2 in the cyclopentanes; H 2 and H 3 in proline numbering), it happens that for solubility reasons (5) and (6) are the only pair that have been run in the same solvent. The change in chemical shift ($CDCl_3$) for H 1 from (5) to (6) is *δ* 2·77[17] to 3·90 (a $\Delta\delta$ of 1·13 ppm) and for H 2 is *δ* 4·50[17] to 5·02 (a $\Delta\delta$ of 0·52 ppm). That is, the proton *α* to the carboxyl is shifted downfield more than twice as far as the carbinol proton upon lactonization.

Experimental

For general experimental details, see Part I.

cis-*2-Hydroxycyclopentanecarboxylic Acid* (*5*)

Ethyl 2-oxocyclopentanecarboxylate (20 g) was prepared by the method of Linstead and Meade,[18] b.p. 84–86°/2 mm (lit.[18] 102°/11 mm); p.m.r. *δ* (neat) 1·20, t, CH_2CH_3; 1·7–2·5, m, $(H3)_2$, $(H4)_2$, $(H5)_2$; 3·10, m, H 1; 4·10, q, CH_2CH_3. The ketone (10 g) was hydrogenated over Adams catalyst and the mixed ethyl *cis*- and *trans*-2-hydroxycyclopentanecarboxylates (7·5 g) were converted into their 3,5-dinitrobenzoates according to the procedure of Pascual and Castells.[19] Attempted fractional crystallization from ethanol gave the *cis*-3,5-dinitrobenzoate (6·2 g) as yellow crystals, m.p. 116–117° (lit.[19] white needles, 116·0–116·8°); p.m.r. *δ* ($CDCl_3$) 1·15, t, CH_2CH_3; 1·5–2·5, m, $(H3)_2$, $(H4)_2$, $(H5)_2$; 3·00, m, H 1; 4·08, q, CH_2CH_3; 5·67, m, H 2; 8·9–9·2, m, ArH. Concentration of the mother liquor gave a second crop (2 g) of the *cis*-derivative, m.p. 116–117°, and we obtained no crystalline *trans*-derivative, contrary to the results of Pascual and Castells.[19]

The *cis*-3,5-dinitrobenzoate (5 g) was converted[19] into ethyl *cis*-2-hydroxycyclopentanecarboxylate, the purity of which was checked by comparing its p.m.r. parameters with those reported by Baumann, Franklin and Möhrle.[17] Saponification of the ethyl ester in 0·5 M sodium hydroxide[19] afforded *cis*-2-hydroxycyclopentanecarboxylic acid (5) (160 mg) which was recrystallized from ether, m.p. 51–53° (lit.[19] 52–53·4°). Its purity was also confirmed by comparing p.m.r. parameters with those described by Baumann *et al.*[17]

[16] Hudson, C. B., Robertson, A. V., and Simpson, W. R. J., *Aust. J. Chem.*, 1968, **21**, 769.
[17] Baumann, H., Franklin, N. C., and Möhrle, H., *Tetrahedron*, 1967, **23**, 4331.
[18] Linstead, R. P., and Meade, E. M., *J. Chem. Soc.*, 1934, 935.
[19] Pascual, J., and Castells, J., *J. Am. Chem. Soc.*, 1952, **74**, 2899.

trans-*2-Hydroxycyclopentanecarboxylic Acid* (*7*)

Cyclopentene was converted into methyl *trans*-2-hydroxycyclopentanecarboxylate by the method of Pascual and Vinas.[20] We record here p.m.r. details for the intermediates. *trans*-2-Chlorocyclopentanol, b.p. 100–101°/15 mm (lit.[20] 81–82°/15 mm); p.m.r. δ (neat) 1·4–2·5, m, $(H3)_2$, $(H4)_2$, $(H5)_2$; 3·9–4·4, m, H1 and H2; 5·70, s, OH. *trans*-2-Hydroxycyclopentanecarbonitrile, b.p. 138–140°/19 mm (lit.[20] 136–137°/18 mm); p.m.r. δ (neat) 1·5–2·4, m, $(H3)_2$, $(H4)_2$, $(H5)_2$; 2·7, m, H1; 3·45, s, OH; 4·45, m, H2. Two-stage hydrolysis[20] of the nitrile via the hydrochloride of the methyl ester of the carboximidic acid gave methyl *trans*-2-hydroxypentanecarboxylate whose purity was confirmed by comparison of p.m.r. parameters with those recorded by Baumann *et al.*[17]

The methyl ester (500 mg) was hydrolysed in 0·5 M sodium hydroxide as for the ethyl ester[19] to yield *trans*-2-hydroxycyclopentanecarboxylic acid (7) (410 mg) which was recrystallized from ether, m.p. 68–70° (lit.[19] 68·3–69·0°). The sample had the p.m.r. parameters recorded by Baumann *et al.*[17]

Reactions of cis- *and* trans-*2-Hydroxycyclopentanecarboxylic Acids* (*5*) *and* (*7*) *with Tosyl Chloride*

(i) The *cis*-hydroxy acid (5) (150 mg, 1·15 mmol) in dry pyridine (1 ml) was treated with tosyl chloride (250 mg, 1·31 mmol) in pyridine (1 ml) at 5°. Next day the reaction mixture was poured into 2 M HCl (10 ml) at 0°. The crude product precipitated as an oil and it was recovered by ether extraction. Purification was effected by preparative t.l.c. in ethyl acetate. The major component (R_F 0·8) was a thick oil which proved to be the β-lactone cis-*cyclopentane-1,2-carbolactone* (6) (50 mg, 39%) (Found: *m/e* 112·0522. $C_6H_8O_2$ requires mol. wt, 112·0524). ν_{max} (liquid film) 1824 cm^{-1}. P.m.r. δ ($CDCl_3$) 1·1–2·5, m, $(H3)_2$, $(H4)_2$, $(H5)_2$; 3·90, m, H1; 5·02, m, H2; the H1 multiplet was complex with a bandwidth between the outside lines of 10 Hz, and the H2 multiplet was essentially a 1 : 2 : 1 triplet with a bandwidth of 7 Hz.

The identity of the minor component (R_F 0·1) was not established.

(ii) Similar treatment of the *trans*-hydroxy acid (7) (130 mg, 1 mmol) in pyridine (1 ml) with tosyl chloride (220 mg, 1·15 mmol) in pyridine (1 ml) gave a solid product when the reaction mixture was poured into aqueous acid. It was filtered off and treated with ether. Most of the material dissolved except for a small amount which was filtered off. The residue from the filtrate was recrystallized from ethyl acetate and identified as cyclopent-1-enecarboxylic acid (8) (56 mg, 53%), m.p. 118–119° (lit.[21] 119°). Its p.m.r. spectrum was identical to that of an authentic sample prepared by isomerization[21] of cyclopent-2-enecarboxylic acid:[1] δ ($CDCl_3$) 1·98, quintet, $(H4)_2$; 2·4–2·8, m, $(H3)_2$, $(H5)_2$; 6·92, narrow m, H2; 9·2, s, CO_2H. ν_{max} (Nujol) 1675 cm^{-1}.

cis- *and* trans-*3-Hydroxy-*DL*-prolines* (*9*) *and* (*10*)

The following modification of the method of Sheehan and Whitney[2] was evolved. 5-Phthalimidopent-2-enoic acid, prepared by the method of Baker *et al.*,[22] m.p. 191–199° (lit.[22] 189–200°), was converted into its 3-methoxy-2-mercuric acetate complex.[2] We observed that the solubility of the complex changed dramatically over several days. Fresh complex was readily soluble in chloroform and in aqueous potassium bromide, but after a few days became insoluble and therefore unsatisfactory for the next step. The fresh complex (6 g) was immediately dissolved by gentle warming in a solution of potassium bromide (2·3 g) in water (23 ml). A small amount of insoluble material was filtered off. The filtrate was cooled in ice and a solution of potassium bromide (2·3 g) and bromine (2 g) in water (3·5 ml) was added slowly with exposure to sunlight until an almost clear yellow solution was obtained. A small amount of insoluble gum was removed by extraction into ether. In order to obtain sufficient quantities of the required product it was found better to repeat the reaction five more times than to perform it on six times the scale.

The combined aqueous fractions from six reactions as above were worked up as described[2] to obtain 2-bromo-3-methoxy-5-phthalimidopentanoic acid as a colourless oil (26 g) that became solid but not crystalline on digestion with pentane.[2] Trituration with hot toluene left Sheehan and Whitney's crystalline diastereomer 'IIa' (8 g), m.p. 149–151° (lit.[2] 149–150°). P.m.r. δ (C_5D_5N) 2·2–2·8,

[20] Pascual, J., and Vinas, J., *Bull. Soc. Chim. Fr.*, 1960, 1430.
[21] Branner-Jørgensen, S., and Berg, A., *Acta Chem. Scand.*, 1966, **20**, 2192.
[22] Baker, B. R., Schaub, R. E., Querry, M. W., and Williams, J. H., *J. Org. Chem.*, 1952, **17**, 77.

m, $(H4)_2$; 3·54, s, OMe; 3·9–4·4, m, H3, $(H5)_2$; 5·08, d, H2, $J_{2,3}$ 6·5 Hz; 7·6–8·0, m, ArH. It was contaminated with about 5% of the other diastereomer.

Concentration of the toluene mother liquor gave a thick oil (16 g) which failed to crystallize (cf. Sheehan and Whitney's substance 'IIb', m.p. 108–111°). P.m.r. showed it was a mixture of the compound above (5 parts) and its diastereomer (4 parts) which had diagnostic signals at δ (C_5D_5N) 3·62, s, OMe; and 5·03, d, H2, $J_{2,3}$ 6·5 Hz. Once it was realized that the toluene trituration did not afford a clean separation, this approach was abandoned.

The solid mixture of diastereomers from the pentane digestion of 2-bromo-3-methoxy-5-phthalimidopentanoic acid (10 g) was converted into a mixture of *cis*- and *trans*-3-methoxyprolines, and these isomers were separated by fractional cyrstallization of their copper salts from ethanol.[2] Carboxylate absorption of the separated salts was characteristic: the *cis*-salt (1·5 g) had ν_{max} (Nujol) 1600 cm^{-1}, and the *trans*-salt (1·0 g) had ν_{max} (Nujol) 1625 cm^{-1}.

The copper salt of *cis*-3-methoxyproline (1·5 g) in ethanol (5 ml) was decomposed with H_2S. Cupric sulphide was removed by filtration with the aid of Celite. The colourless solution was evaporated to leave *cis*-3-methoxyproline (630 mg) as an oil which was immediately refluxed (2 h) with constant-boiling HBr (5 ml). The mixture was evaporated to dryness and the residue in water (1 ml) was percolated through a column of Dowex 50W-X8 ion exchange resin (3 g) in the H^+ form. The column was washed thoroughly with water and then the amino acid was eluted in 2 M NH_4OH. Removal of solvent and recrystallization of the solid residue from ethanol–water gave *cis*-3-hydroxy-DL-proline (9) (350 mg) as off-white crystals, m.p. 225–232° (dec.) (lit.[2] 225–235° (dec.)), which had the correct p.m.r. spectrum.[11]

The same procedure applied to the copper salt of *trans*-3-methoxyproline (1·0 g) gave *trans*-3-hydroxy-DL-proline (11) (210 mg) as off-white crystals, m.p. 224–232° (dec.) (lit.[2] 224–230° (dec.)), which had the correct p.m.r. spectrum.[11]

cis- *and* trans-*3-Hydroxy*-N-*tosyl*-DL-*prolines* (*10*) *and* (*12*)

These known[3,4] compounds were prepared by standard methods, and some comments and details including p.m.r. data are included in Part III.[5]

Reactions of cis- *and* trans-*3-Hydroxy*-N-*tosyl*-DL-*prolines* (*10*) *and* (*12*) *with Tosyl Chloride*

(i) The *cis*-hydroxy acid (10) (15 mg, 0·050 mmol) in dry pyridine (0·2 ml) was treated with tosyl chloride (19 mg, 0·10 mmol) at 5°. Next day 1 M HCl (3 ml) at 0° was added and a crystalline precipitate was obtained upon vigorous scratching. After being collected the solid recrystallized from benzene–cyclohexane to yield the *β*-lactone cis-N-*tosylpyrrolidine-2,3-carbolactone* (13) (13 mg, 95%) as colourless crystals, m.p. 112–114° (Found: C, 53·8; H, 5·05; N, 4·8; S, 10·9; *m/e* 233·066. $C_{12}H_{13}NO_4S$ requires C, 53·9; H, 4·9; N, 5·2; S, 11·9%. $C_{11}H_{13}NO_2S$ ($M-CO_2$) requires mol. wt, 233·067). ν_{max} 1847 cm^{-1}. P.m.r., see Discussion.

(ii) The *trans*-hydroxy acid (12) (15 mg, 0·050 mmol) was unchanged after treatment with tosyl chloride (19 mg, 0·10 mmol) in pyridine (0·2 ml) at 5° overnight.

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