PREPARATION AND RATES OFALKALINE HYDROLYSIS OF
CIS- AND TRANS-5,6-TETRAMETHYLENEDIHYDROURACILS

I. G. Pojarlieff, R. Z. Mitova-Chernaeva, I. Blagoeva, B. J. Kourtev

(Submitted by Academician D. Ivanov on November 13, 1967)

Previous work on the cyclization of diastereomeric β-ureido acids \([Ia,b]\) and acid \([lb]\) and alkaline \([2]\) hydrolysis of 5,6-disubstituted dihydrouracils showed that the results could be best interpreted by including the effect of certain planarity of the dihydrouracil ring, more particularly the increased strain between the two cis substituents, among the considerations. Planarity of this ring system has also been invoked to explain UV, pK\([3]\) and NMR\([4]\) data. In order to assay further this effect in terms of chemical reactivity, the cis and trans isomers of 5,6-tetramethylenedihydrouracil (III) were investigated. The results obtained so far are reported in the present paper. Both isomers of III were obtained by usual methods \([5, Ia]\).

The configurations of the parent hexahydroanthranilic acids (I) were determined by \([6]\) and unequivocally confirmed \([7]\) by means of the Hofmann rearrangement of cis hexahydrophthalamic acid. We used the latter method for the preparation of cis I. The preparation of trans I by the reduction of anthranilic acid according to Einhorn is cumbersome and, in spite of using anhydrous amyl alcohol \([6]\), gave, in our hands, low yields. A more convenient method of obtaining trans I is by isomerizing cis I, under the conditions described in \([6]\), which gave a 30\% yield.

Both amino acids gave two different 2-ureidocyclohexanecarboxylic acids (II) in over 70 yields which proves the retention of configuration at this stage; consequently, the ureido acid with m. p. 194-5° obtained from cis I is of cis configuration and the ureido acid with m. p. 177-9° — of trans configuration.

Heating both isomers of II in 1:5 HCl at 90° for one hour led to two different dihydrouracils in high yields (Table). These in turn gave the respective initial ureido acids on hydrolysis in N/2 NaOH, thus proving reten-
tion of configuration along the transformation. On these grounds the 5,6-
tetramethylenedihydrouracil with m. p. 242.4° has cis configuration and
that with m. p. 255.8° — trans configuration. The observed ease of ring
closure of both isomers of II indicates that the ring system of III is formed without any con-
siderable strain, even in case of the trans
fused compound (e. g. [14] erythro 3-ureido-2,3-
diphenylpropionic acid cyclizes only 33% for 5 h
at 115°).

In a previous work [14] on the cyclization
in HCl of diastereomeric β-ureido acids it was
shown that this reaction proceeds in the case
of α,β-diaryl compounds stereoselectively* to
the trans dihydouracil, in the case of α,β-dialkyl
substituted β-ureido acids isomerization is less
facile and conditions could be found for a ste-
reospecific reaction (lower temperatures and
acidity). A novel feature of III is their confi-
gurational stability under conditions which
caused considerable isomerization in the case
of 5,6-dimethyldihydrouracil.

Fig. IR-spectra of 5,6-tetra-
methylenedihydrouracil

<table>
<thead>
<tr>
<th>cis-1</th>
<th>trans-1</th>
<th>cis-trans-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>3520</td>
<td>3350</td>
<td>3450</td>
</tr>
<tr>
<td>3450</td>
<td>3520</td>
<td>3350</td>
</tr>
</tbody>
</table>

When both isomers of III, obtained from the cyclization reaction, were
crystallized from ethanol or water, their melting points decreased instead of
increasing. While a similar lowering of the m. p. was observed in the case
of the two 5,6-dimethyldihydrouracils [14], in the present case the lowering is
quite significant, 8—10°, and the melting point remains more or less the same
on further recrystallization. When refluxed in 1:5 HCl in the attempted iso-
erization experiments, the m. p. of III rose to those of the initial products.
The IR-spectra shown in the Fig. demonstrate that all samples are free from
the other isomer (compare the peak at 485 cm⁻¹ of the cis compound and
that at 465 cm⁻¹ of the trans one). Both raw products show a rather weak
peak at 452 cm⁻¹, which is slightly more pronounced in the recrystallized
samples and disappears in the samples treated with HCl. No trace of this
peak was observed either in samples from reaction mixtures refluxed for three
hours. This behaviour is probably due to some admixture but its amounts
seem negligible, as the low melting products gave good analysis.

Finally, a study was made of the rate of hydrolysis in 0.1 N NaOH at
25° of both isomers of III. The trans isomer was found to hydrolyse 5.8 times
faster than the cis one (the first order rate constants observed were
ktrans = 8.58.10⁻⁴ sec⁻¹ and kcis = 1.49.10⁻⁴ sec⁻¹). The mechanism of alka-
line hydrolysis of dihydouracils may be assumed to proceed similarly to
that of 2-thiohydantoins [9] by an attack of OH⁻ on the unionized molecules:

* Stereoselectively and stereospecifically in the sense used by E. L. Eliel in „Stereo-
In such a case structure $B$ should approximately represent the transition state. In 0.1 N NaON dihydouracils may be expected to be completely ionized\[9\], so that the anion $A$ may be considered as the ground state. Considering only chair conformations, there is only one conformation possible for the $trans$ compound and two for the $cis$ one; these later are probably of rather similar energy in the ground state; in the supposed transition state the conformation with $C(OH)\sup{\Theta}$ equatorial is undoubtedly preferred. An estimate of the contribution to $\Delta H^\# (\Delta H^\#cis - \Delta H^\#trans)$ due to steric interactions was made by examining models. Taking into account only the $N(1)$ axial conformations of the $cis$ isomer, neglecting bond angle distortions and further equating $\angle N$- to $\angle NH$, $\angle C(OH)\sup{\Theta}$ to $\angle C(OH)\sup{\Theta}$, etc. this contribution was found to be rather small: $[\text{CH}_2: \text{CO}] - [\text{CH}_2: \text{OH}]$. The value of the first interaction was estimated\[10a\] as 0.2 kcal/mol, and that of the second one\[10b\] as 0.35, i.e. indicating a slightly more unfavourable enthalpy for the $trans$ isomer. This may be thought to be outweighed by some loss of entropy of mixing in the case of the $cis$ isomer but this (c. a. 0.4 kcal/mol) would still fall short of the observed difference in rates (equivalent to c. a. 1 kcal/mol in $\Delta F^\#$). Notwithstanding the uncertainty of the above analysis, it suggests, in our opinion, that this difference in rate may in the main part be attributed to the greater strain in the ground state of $trans$ III due to the planarity of the ring in the anion.

**EXPERIMENTAL.**\* $\text{Trans-Hexahydroanthranilic Acid.}$ 4.0 g of $cis$ I (obtained according to\[7\] from commercial $cis$ hexahydrophthalic anhydride) in 30 ml of conc. HCl were heated for 10 hours at 196-9°. On cooling an oil separated, which was extracted with ether. The ether extract, partially soluble in 10% NaOH, was discarded. The aqueous layer was evaporated in vacuo, the dry residue dissolved in a small amount of water and passed through a column with cationite in H$^+$-form (Wofatit KPS 200), the column washed with water and eluted with IN NH$_3$. The dry residue of the ammonia eluate (2.5 g) was dissolved on heating in 90% ethanol, filtered, the solution concentrated and precipitated with acetone, 1,26 g, m. p. 264-5°. Recrystallized from methanol m. p. 265-6° (Kofler Microscope 268-9°, lit.\[6\] 273°). Melted at the same temperature, it showed no lowering of the m. p. of a mixture with a sample obtained according to E in h or n\[9\]. Concentration and further precipitation with acetone of the mother liquors of 1.26 g yielded low melting fractions, apparently of mixtures of the two isomers.

$\text{2-Ureidocyclohexanecarboxy Acids.}$ 4.0 g of $I$ ($cis$ or $trans$) were dissolved in 20 ml of water and 4.8 g of KOCl were added and heated for 1 hour at 80°. On cooling, the solution was acidified with 1:1 HCl to pH 3 and

\* All melting points are in capillary and uncorrected unless stated otherwise. Elementary analyses were carried out by the analytical laboratory at the Inst. of Org. Chem., Bulg. Ac. Sci. IR-spectra were taken in Nujol on a UR 10 Carl Zeiss-Jena Spectrophotometer.

133
allowed to stay 2–3 hour in the fridge. The precipitate was collected and dried in vacuo at 50°. The ureido acids thus obtained melted only 1–2° lower than the crystallized samples (Table).

5,6-Tetramethylenedihydrouracils. A solution of the respective II in 1:5 HCl (trans - 2.7% and cis - 0.6%) was heated for one hour at 90°. III crystallized on cooling. Best purified by refluxing for 1-2 h. in 1:5 HCl (Table).

Alkaline Hydrolysis of III. 0.0004 mol of III were dissolved by gently warming to 30-40° in 4 ml of 2% NaOH and left overnight. II was isolated as above described. Yields: cis - 74%; trans - 61%; pure as judged by m.p. and mixed m.p.

Attempted Isomerization of III. 0.0500 g of III were refluxed in 5 ml of 1:5 HCl for 4 hours. On cooling, nearly 80% of III could be collected in the cases of both isomers. See discussion above and the Figure.

Table

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>m. p. °C</th>
<th>Equil. wt.</th>
<th>N%</th>
<th>Calc. Found</th>
<th>tCOOH-1</th>
<th>tNH2-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis</td>
<td>84</td>
<td>194–5(ETOH)</td>
<td>185.8</td>
<td>15.4</td>
<td>1560#</td>
<td>3335</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>77</td>
<td>177–9(H2O)</td>
<td>187.8</td>
<td>14.8</td>
<td>1595#</td>
<td>3342</td>
<td></td>
</tr>
<tr>
<td>trans</td>
<td>85</td>
<td>242–4(1:5 HCl)</td>
<td>167.6</td>
<td>16.7</td>
<td>1700#</td>
<td>3225#</td>
<td></td>
</tr>
<tr>
<td>cis</td>
<td>95</td>
<td>255–8(1:5 HCl)</td>
<td>16.6</td>
<td>16.8</td>
<td>1670#</td>
<td>3070#</td>
<td>3190#</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3312#</td>
</tr>
</tbody>
</table>

# amide II; # broad.

Kinetic Procedure. The reaction was followed by measuring the decrease of optical density at 2300 Å (absorption due to the anion of III, εcis = 6.0.10^3; εtrans = 6.2.10^3) with a Carl Zeiss-Jena U1 Spectrophotometer in a temperature controlled cell unit. Rate constants were obtained by the least-squares treatment of log E vs. time plots.

Institute of Organic Chemistry
Bulgarian Academy of Sciences, Sofia

REFERENCES


134