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CONFIGURATIONAL STABILITY OF THE CHIRAL CENTRE C(3) IN SOME 1,4-BENZODIAZEPIN-2-ONES

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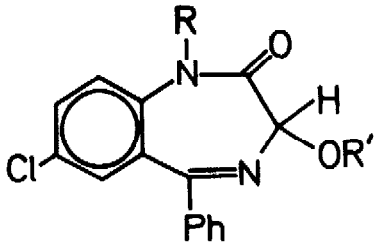
Our interest in elucidating the stereospecificity of *in vivo* biological activity (1,2) and enzymatic biotransformations (3) of some chiral 1,4-benzodiazepin-2-ones has led to the preliminary determination of *in vitro* configurational stability of the chiral centre C(3) in some C(3)-alkyl, C(3)-O-alkyl or O-acyl and C(3)-ammonio-substituted 1,4-benzodiazepin-2-ones (4). These results are of obvious biological importance, suggesting conceivable therapeutic advantages of administration of enantiomerically pure compounds as a worth-while research goal. At least three different mechanisms could be proposed for the observed racemization i.e. (a) acid catalyzed C(3)-H/D exchange, (b) ring-chain tautomerisms, for 3-hydroxy derivatives only, and (c) solvolytic identity reaction (degenerate nucleophilic exchange, i.e. exchange of the same groups).

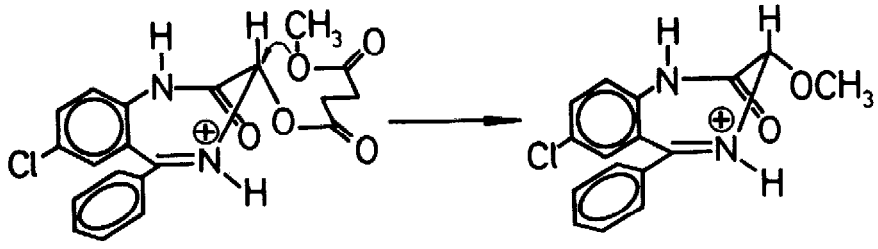
Here we discuss a possible mechanism, leading to high retention of configuration in the acid catalyzed methanolysis of (+)-1a, firstly observed by Corbella et al. (5), and subsequent identity reaction as a cause for racemization of (+)-1b formed. Methyl-d_3-derivatives (±)-1d and (±)-1e have been prepared (6) and subjected to methanolysis (0,03M HCl in MeOH at 25°), in order to exclude preetherification by an intramolecular front-side attack of the carbomethoxy group in the intermediately formed double-ester (+)-1c, which is a pathway leading to high incidence of retention. Aliquots were quenched at 0,5-hr intervals in aqueous acetate (4 samples), and products were quantitatively separated by chromatography on

silica gel column.



	R	R'		R	R'
1a	H	$OC(CH_2)_2COOH$	1f	CH_3	CH_3
b	H	CH_3	g	H	CD_3
c	H	$OC(CH_2)_2COOCH_3$	h	H	H
d	H	$OC(CH_2)_2COOCD_3$	i	CH_3	H
e	CH_3	$OC(CH_2)_2COOCD_3$			

Nmr analysis of the N(1)-CH_3/C(3)-CH_3 ratio starting from 1e, and the C(3)-H/OCH_3 ratio starting from 1d, revealed exclusive OCH_3 incorporation i.e. the formation of (±)-1b and 1f by intermolecular exchange (solvolysis).



The same result emerged from solvolytic experiments with 1c in CD_3OD. Rate constants are given in Table 1.

Table 1. Rate constants for Solvolysis 1c ⟶ 1g (at 35,0±0,2°C)

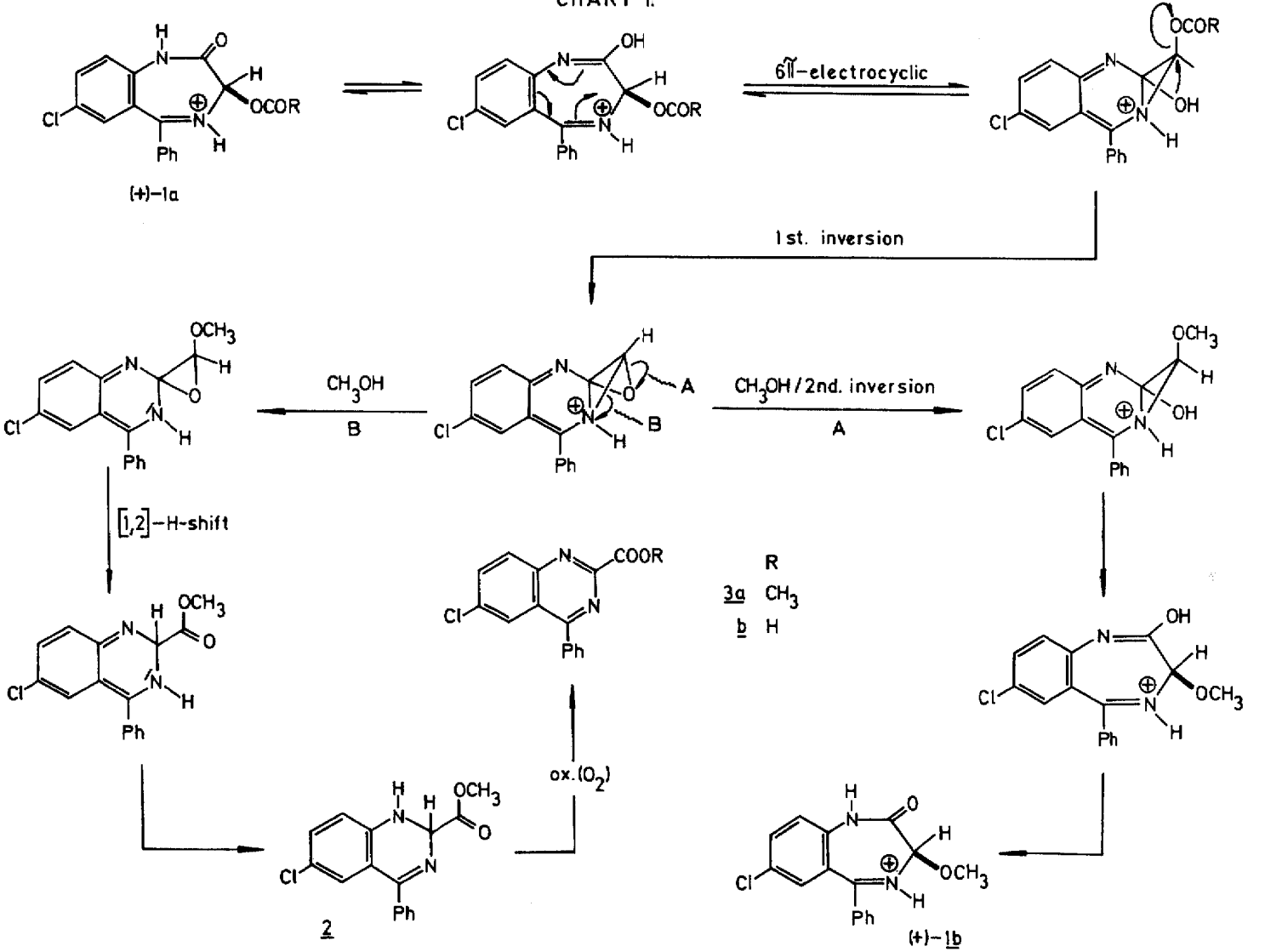
Run no.	mmol of 1c	1c/CF_3COOH (mol/mol)	Solvent	Solvolysis rate (k_s x 10^4 s)
1	0,23	0,29	$CD_3OD/CDCl_3$(1:1)	1,36±0,14
2	0,18	0,23	CD_3OD	2,68±0,37
3	0,14	0,21	CD_3OD	2,17±0,38
4	0,08	0,20	CD_3OD	0,89±0,11

During nmr kinetic measurements no shift of R-$COOCH_3$ protons within 1c (at 3,68 ppm) to C(3)-OCH_3 within 1b (at 3,62 ppm) was observed, i.e. only 1g was formed. Thus, no formation of (±)-1b and consequently no intramolecular methoxylation within 1c could be ascertained.

The only tlc-observable spot in these experiments was from a side-product identified as 2 from spectroscopic data and by conversion to 3a and to previously described 3b (7).

All experimental facts could be best explained by the mechanistic scheme presented in Chart 1. It became obvious once more, that retention of configuration as in (+)-1b, should be explained by traditional double-inversion. However,

CHART 1.


(+)-1a
6π-electrocyclic
1st. inversion
CH3OH
B
CH3OH / 2nd. inversion
A
[1,2]-H-shift
ox.(O2)
R
3a CH3
b H
2
(+)-1b

occurence of the S_N2-type reaction at the small rings, with retention was theoretically predicted (8), and seem to have been recently proved (9). We regard acid catalysis of the solvolysis of (+)-1a as an indication that highly basic protonated aziridine intermediate is formed, as one of the fluctuating structures in electrocyclic equilibrium with the imide form. Racemization of the product (+)-1b presumably occurs by concurrent front-side attack of the solvent molecules on the tricyclic system within the intermediate. Kinetic data for racemization revealed no dependence on hydrogen chloride concentration down to equimolarity, indicating that no nucleophilic competition of the chloride anion with solvolysis occurs. Usual temperature dependence was found for racemization between 20° and 45°, as revealed by thermodynamic parameters: $\Delta S=7,2\pm 2,5$ e.u., $\Delta H=18\pm0.8$ kcal/mol.

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References and Notes

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