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Chiral 1,4-Benzodiazepines. X.[1] Further Investigations of Configurational Stability of the Chiral Centre C(3)

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For various at C(3)-chiral 1,4-benzodiazepin-2-ones rate determinations of racemisation (k_α- for C(3)-OCH_3 derivative (+)-*1*), degenerate nucleophilic exchange (k_c- for rac. *1* and rac. *2*), and solvolysis (k_s- for C(3)-hemisuccinyl derivative *4*) have been performed. These investigations revealed; (*a*) retention of configuration during methanolysis of (+)-*3*, (*b*) slow racemisation of (+)-*1* during solvolytic degenerate nucleophilic substitution ($k_c/k_\alpha \sim$ $\sim$ 4), (*c*) no participation of S_N1 retentive reaction, possible via intramolecular transfer of the methoxy group within intermediary compounds *4*—*6*, (*d*) thermodinamic parameters for racemisation of (+)-*1* between 20—40 °C; $\Delta H^{\neq} = 18.0 \pm 0.8$ kcal/moll**, $\Delta S^{\neq} =$ $= -7.2 \pm 2.5$ e. u.*** Mechanistic scheme is offered which accounts for all experimental results. The effect of the electrocyclic equilibrium on the electronic structure of N(4) protonated benzodiazepines, and its possible consequences for their mechanisms of biological activity on the central nervous system (CNS), have briefly been discussed.

INTRODUCTION

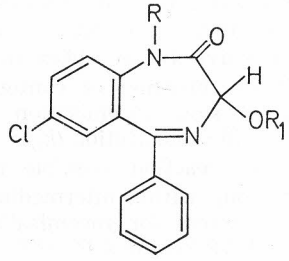
Recently[2,3] we discussed mechanisms likely to be involved in acid-catalysed solvolytic racemisation of various 3-substituted 1,4-benzodiazepin-2-ones at the C(3)-chiral centre. We now wish to present further investigations of acid-catalysed solvolysis which led to some speculation on the fluctuating electronic structures arising upon protonation at N(4). Such structures may hold implications worth considering in discussion of biological effects produced by various 1,4-benzodiazepin-2-one derivatives.

The three different mechanisms proposed by us[2] as potential routes of racemisation in acid-catalysed solvolysis were (*a*) C(3)-H/D exchange, (*b*) ring-chain tautomerism (for 3-hydroxy derivatives), and (*c*) the identity reaction, i. e. degenerate nucleophilic substitution (for 3-alkoxy derivatives). Recent reports by other authors[4-6], however, suggest that bimolecular nucleophilic substitutions might occur *with retention of configuration,* taking their way over an intermediate with a five-coordinated carbon atom. We thought that this may be the way followed by acid-catalysed methanolysis of the hemisuccinyl

** 1 kcal = 4.184×10^3 J
*** e. u. = 4.184 J K^{-1} mol^{-1}

ester (+)-*3* which was recognized to occur with retention of configuration[7], a result we were able to confirm[2].

We found previously that acid-catalysed solvolyses of several 3-(quat. ammonio)-substituted 1,4-benzodiazepin-2-ones result in racemisation by a mechanism of H/D exchange[2]. The same was found with one (3*R*)-phenyl derivative[8], accompanied by a rapid loss of optical activity. The question of whether racemisation of 3-hydroxy derivatives partly occurs by the mechanism of ring-chain tautomerism as assumed[2] will be the subject of a future paper. Presently we shall describe a study of kinetics and mechanism of degenerate exchange suggested[2] for acid-catalysed solvolysis in the 3-alkoxy series of 1,4-benzodiazepin-2-ones. In this study we used the methoxy derivatives *1*—*2* and *7*—*8*, and additionally the 3- hemisuccinyl derivatives *3*—*6* (intended to represent the class of 3-acyloxy derivatives). A survey of these compounds is given in general formula below, details about their preparations are given in the Experimental.



	R	R_1
1	H	CH_3
2	CH_3	CH_3
3	H	$COCH_2CH_2COOH$
4	H	$COCH_2CH_2COOCH_3$
5	H	$COCH_2CH_2COOCD_3$
6	CH_3	$COCH_2CH_2COOCD_3$
7	H	CD_3
8	CH_3	CD_3

RESULTS AND DISCUSSION

The replacement of a C(3)-alkoxy group effected by acid-catalysed alcoholysis was studied kinetically in considerable detail so as to obtain a better insight into the mechanism of degenerate nucleophilic substitution. The time course of substitution was followed by two techniques: NMR technique was used with racemic *1* and *2*, and polarimetric technique with the dextrorotatory enantiomer of the former, (+)-*1*. The results of rate determinations are summarized in Tables I (polarimetric) and II—IV (NMR).

The following results were derived from polarimetrically and NMR determined rate constants k_α, and k_e, respectively.

(*a*) Thermodynamic activation parameters were calculated on the basis of temperature dependence of k (runs no. 12—18 in Table I). The values obtained, $\Delta H^{\neq} = 18.0 \pm 0.8$ kcal/mol and $\Delta S^{\neq} = -7.2 \pm 2.5$ e. u. per mol, are such as to leave open the question of molecularity for the rate-determining step[9].

(*b*) In experiments with compounds *1* and *2* the rate constants k_e obtained at 35 °C (runs no. 4 in Table III and Table IV) could be compared with k_α's obtained for (+)-*1* under nearly same C_{H^+}/C_B ratio and temperatures (runs no. 3, 16 and 17 in Table I). They give k_e/k_α ratios of 3.40, 4.62 and 3.29, respectively. We assume that an extrapolated value of about 4, i. e. one *cum.*-inversion of

TABLE I

Racemisation Rates of (+)—1 (c = 50.0 mg/5.00 ml MeOH/HCl)

Run no.	c_{H^+}/c_B M/M	t/°C	$k \times 10^4$/s	Run no.	c_{H^+}/c_B	t/°C	$k \times 10^4$/s
1	0.0371	28.0	1.05 ± 0.04	10	6.82	44.5	10.30 ± 0.19
2	0.156	35.0	1.43 ± 0.03	11	„	„	10.26 ± 0.22
3	0.809	„	1.98 ± 0.02	12	3.87	21.0	0.86 ± 0.10
4	1.835	„	2.30 ± 0.03	13	„	23.0	1.43 ± 0.02
5	3.242	„	2.55 ± 0.03	14	„	26.5	1.95 ± 0.08
6	6.82	24.5	2.35 ± 0.02	15	„	30.5	2.90 ± 0.04
7	6.82	28.0	2.31 ± 0.03	16	„	33.0	3.81 ± 0.05
8	6.82	28.0	2.57 ± 0.02	17	„	36.0	5.35 ± 0.09
9	6.82	35.0	7.01 ± 0.03	18	„	39.5	7.02 ± 0.12

TABLE II

Rate Constants for Solvolysis 4 → 1 (in CD_3OD/DCl at 35 ± 0.1 °C)

Run no.	c_{D^+}/c_B M/M	$k_s \times 10^3$/s
1	0.245	0.59 ± 0.05
2	0.461	0.71 ± 0.04
3	0.622	1.05 ± 0.06
4	0.893	1.42 ± 0.09
5	1.755	3.06 ± 0.15
6	2.644	5.11 ± 0.18

TABLE III

Rate Constants for the Exchange Reaction 2 → 8 (in CD_3OD/DCl at 34.5 ± 0.2 °C)

Run no.	c_{D^+}/c_B M/M	$k_e \times 10^3/s^{-1}$
1	0.791	0.69 ± 0.08
2	1.293	0.71 ± 0.06
3	1.945	1.23 ± 0.11
4	3.889	1.76 ± 0.18
5	7.718	3.89 ± 0.28

configuration pro five degenerate exchanges in (+)-*1* properly reflects relatively high stereoselectivity of this process.

(*c*) As nearly the same values of k_e were obtained with compounds *1* and *2*, the influence of N(1)-substitution upon the rate of solvolysis can only be very weak.

(*d*) With compound *4* somewhat larger k_e values (Table II) were found than with *1* and *2*. This obviously means that acyloxy is a better leaving group than alkoxy. In experiments with *4* the NMR recordings showed no shift from the singlet at 3.68 ppm characteristic of ... $COOCH_3$-protons to that at 3.63 ppm characteristic of ... OCH_3-protons, but instead a singlet appeared at 2.63 ppm

TABLE IV

Rate Constants for the Exchange Reaction $1 \rightarrow 7$ *(in* CD_3OD/DCl *at* $35.0 \pm 0.1\,^{0}C$*)*

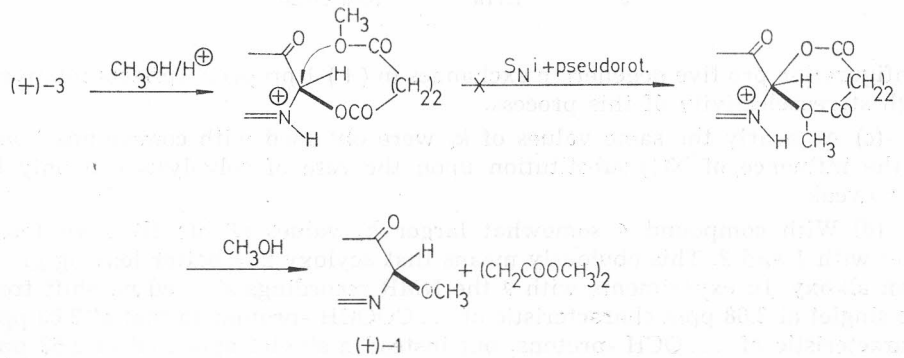
Run no.	c_{D^+}/c_B M/M	$k_e \times 10^3/s^{-1}$
1	0.685	0.50 ± 0.08
2	0.722	0.54 ± 0.06
3	0.722	0.53 ± 0.04
4	0.806	0.58 ± 0.08
5	0.911	0.65 ± 0.03
6	0.924	0.67 ± 0.07
7	0.924	0.67 ± 0.06
8	1.027	0.72 ± 0.04

(4H). This singlet is characteristic of protons in equivalent methylene groups, which indicates that symmetric dimethyl succinate was formed during solvolysis. Therefore the conversion of *4* to *1* could not include intramolecular transfer of OCH_3 to C(3)-position, but must be solely the result of methoxy transfer from the solvent.

(*e*) Compounds *5* and *6* were subjected to acid-catalysed methanolysis, and samples of the reaction mixture taken at intervals were quenched in aqueous acetate which was followed by quantitative extraction and isolation of the product. Values of NMR-signal ratios for H and OCH_3 bound to C(3) in the product show that in this instance, too, OCH_3 could only have entered by transfer from the solvent. No exchange of H for OCD_3 occured in similar experiments where formation of *7* and *8* failed to occur.

As mentioned in the Introduction, we once regarded the retention of configuration after solvolytic conversion of (+)-*3* to (+)-*1* as being a consequence of an intramolecular S_N-type reaction taking place without configuration change. We assumed that (+)-*3* first undergoes an acid-catalysed esterification to give (+)-*4*, whereupon the methylated acyloxy group pseudorotates from axial position, on pentacoordination at C(3), with subsequent intramolecular transfer of the methoxy terminal and exit of the acyloxy group (Scheme 1). But the results presented under *d* and *e* invalidate this sequence. Furthermore, at the time these results were obtained a group of authors[10,11] reported convincing

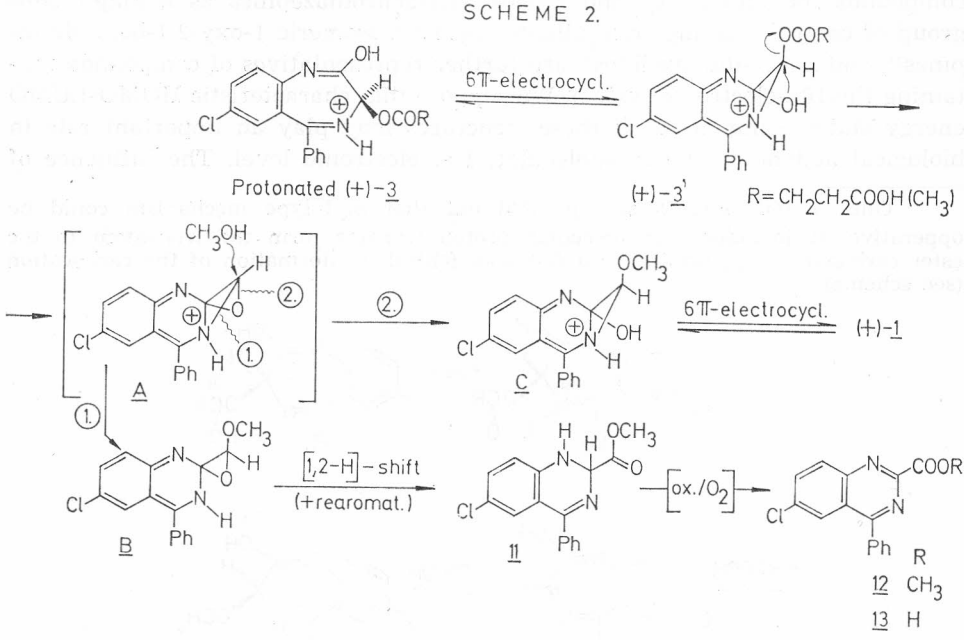
SCHEME 1.



experimental evidence against a participation of pentacoordinated carbon in the configuration-retaining S_N2 mechanism. On the other hand, a monomolecular nucleophilic substitution mechanism should be precluded by the positive charge on the protonated N(4)-atom. It is noteworthy, however, that retentions observed during solvolysis of carbocyclic seven membered analogues of benzodiazepines, i. e. C(9)-substituted tribenzocycloheptatrienes, have been explained by a configuration retaining S_N1 mechanism[12,13]. We think that the retention of configuration in acid-catalysed methanolysis of (+)-*3* is due to two nucleophilic steps each associated with inversion. We also think that this mechanism involving two inversion steps applies to the acid-catalysed solvolysis of (+)-*1* after which configuration was largely retained, contrarily to an expected racemisation by degenerate exchange.

Further details of the mechanism remained unclarified at first. However, we succeeded in isolating trace amounts of a by-product formed in solvolysis of (+)-*3* which helped to better understand the reaction sequence. Spectroscopic evidence suggested structure *11* (Scheme 2) for the by-product in question. This

SCHEME 2.

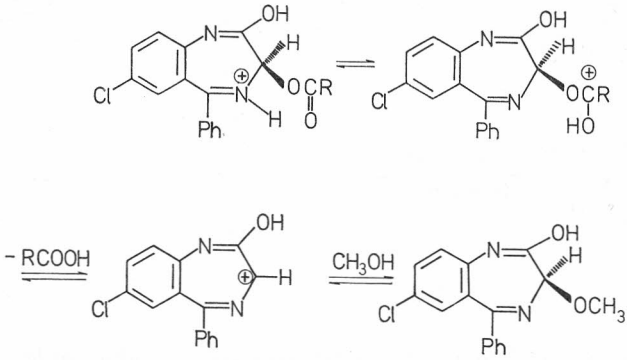


structure was confirmed by oxidation which gave a product of known structure, namely the acid *13*. A mechanism for the acid-catalysed solvolytic conversion of (+)-*3* to (+)-*1* based on these findings is depicted in Scheme 2. In this scheme both *11* and (+)-*1* appear as products stemming from one highly strained intermediate, *A*. The formation of this intermediate is associated with the first inversion which takes place after N(4)-protonation of (+)-*3* and equilibration with a valence tautomer (+)-*3'*. Intermediate *A* contains two three-membered rings, oxirane and aziridine, readily opened by solvolysis. An opening of the aziridine ring (pathway 1) should give compound *B*, and is associated with the second inversion. Therefore *B* returns to the configuration of the starting compound,

(+)-*3*. The opening of the oxirane ring (pathway 2) results in the formation of *C* which also should have the configuration of the starting compound. Both the oxirane[14] and aziridine[15,16] ring systems can, however, be opened with retention of configuration when the reagent attacks from the front side. This mechanism of ring opening might account for the slow racemisation of (+)-*1*, about 80% stereoselectivity found in the solvolytic identity reaction.*

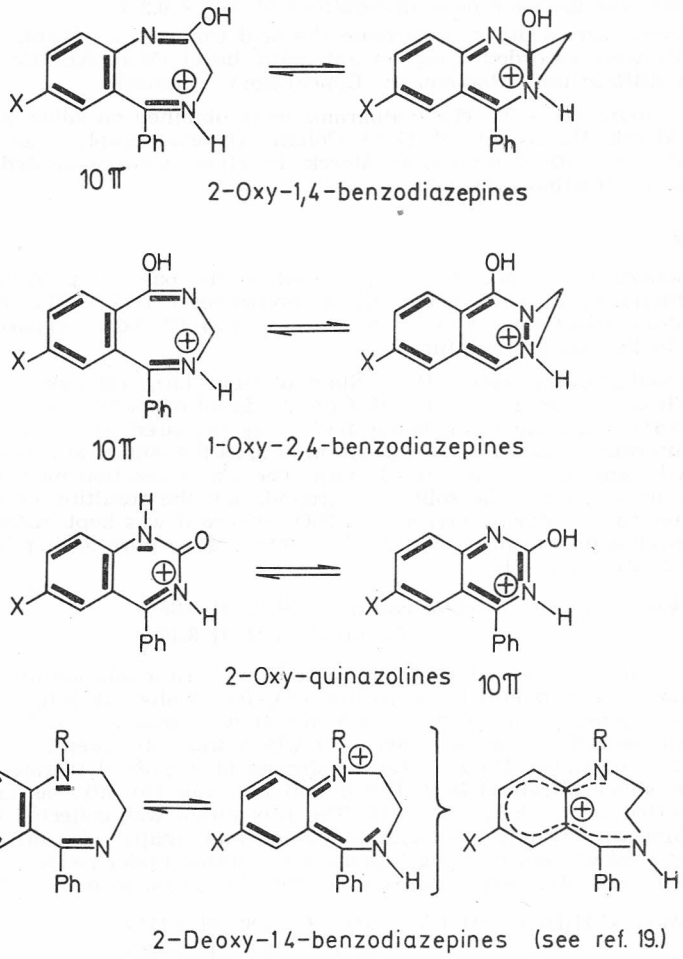
Compound *11* is formed as a result of two consecutive pericyclic reactions: (*1*) electrocyclic 6π-disrotatory[17] ring closure, and (*2*) 1,2-suprafacial proton shift[18]. The electrocyclic equilibrium (valence tautomerisation) (+)-*3* ⇌ (+)-*3′* seems to be induced by N(4)-protonation, as the N(4)-atom should exhibit much stronger electron-donating ability (basicity) within an aziridine ring in the (+)-*3′* form, than in (+)-*3*. This offers a new aspect to MO properties in *3′*, a type of structure regarded previously as an aza-polymethine form of 1,4-benzodiazepines[19]. Namely several structures associated with central tranquilizing activity (see Scheme 3) share a characteristic electronic system. This group of compounds includes 2-oxy and 2-deoxy-1,4-benzodiazepines as a major subgroup of centrally acting tranquilizing agents[20]. Isomeric 1-oxy-2,4-benzodiazepines[21], and 2-oxy-quinazolines[22] are further representatives of compounds containing the 10π-electronic system. We suppose that characteristic HOMO-LUMO energy states common to all these structures may play an important role in biological actions at the submolecular, i. e. electronic level. The influence of

* One of the referees still pointed out that S_N1-type mechanism could be opperative. It includes intramolecular proton transfer form the *N*(4)-atom to the ester carbonyl group, leading to a flat boat (chiral) conformation of the carbocation (see scheme)



Then $k_c/k_\alpha \sim 4$ could mean that stereoselective trapping with methanol, i. e. from the same side of the boat from which the leaving group has gone out, occurs 4 times faster than the ring inversion. We abandoned previously this possibility after consideration of the pronounced negative entropy of the solvolysis, and because of the requirement for nitrogen *N*(4) deprotonation. Namely, its basicity should move along the electrocyclic equilibrium ranging from $pK_a \sim 3$ — in benzodiazepines — to $pK_a \sim 10$ in aziridines, while an excess of the »free« protons in solution remains. We now would like, however, to accept this possibility, and to emphasize that NMR method for kinetic measurements precludes determination of a possible kinetic isotope effect to ascertain exact order of the rate-determining step.

SCHEME 3.



substituents in 5- or 7-position (X and Ph in the Scheme 3) on these energy levels may also serve to explain the marked alterations in central activity observed upon substitution in these position of several benzodiazepines[23] Theoretical and experimental work further elaborating on these ideas is being continued in our laboratories.

EXPERIMENTAL

General. — All m. p.'s were determined on a Kofler microheating stage (Boëtius), uncorrected values are given.

Samples used for spectrometry, polarimetry and elemental microanalyses were previously dried 2 h at room temperature under reduced pressure (0.01 mm Hg).

Apparatus. — Measurements of optical rotation were made at constant temperature using an NPL Model M3D or a Perkin-Elmer Model 141 polarimeter, using double-walled optical cells connected to a VEB type U6 thermostat.

NMR spectra were recorded with a Varian T-60 spectrometer. The same instrument was used for peak integrations at 35 ± 0.1 °C. A Perkin-Elmer M 257 NMR spectrometer was used for peak integrations at 34.5 ± 0.2 °C.

Titrations carried out to determine the acid content of solvents used in kinetic experiments were recorded using an automatic buret (Mod. ABU13) connected to a Titrigraph SBR-2c unit (Radiometer, Copenhagen, Denmark).

Chromatograms. — TL chromatograms were obtained on silica gel Fertigplatten F-257 (E. Merck, Darmstadt, W. Ger.). Column chromatography was run with silica gel (particle size 0.05—2 mm) from Merck. Fractions were separated with an LKB 7000 automatic fraction collector.

Syntheses

Compounds *1*, *2*, *7* and *8* were prepared on the basis of published directions[24], using methanol-d_4 instead of CH_3OH in preparing *7* and *8*. Racemic *3*[25] and its dextrorotatory enantiomer (+)-*3*[25], as well as (+)-*1*[26] were prepared by methods described in the patent literature.

Monomethyl-d_3*-succinate (9).* — Starting from 4.0 g (40 mmol) of succinic anhydride (Fluka: purum, m. p. 119—121 °C) and 2.50 ml of methanol-d_4 (Stöhler, Isotope Chem.,: 99.5% deuterated) the hemiester *9* was prepared by a known procedure[27]. NMR-monitoring indicated a fast formation of *9*, as the singlet at 3.01 ppm $(CH_2CO)_2O$ disappeared completely within 10—15 min. The warm reaction mixture was allowed to solidify in a mortar. The solid was ground, and the resulting crystalline powder was transferred to a drying vessel over P_2O_5, where it was kept overnight at 0.1 mm Hg. Recrystallization from carbon disulfide-ether gave pure *9*, m. p. 51—53 °C. NMR ($CDCl_3$): 2.70 (broad s, 4H).

Anal. $C_5H_4D_4O_4$ (136.15) calc'd.: C 44.11, H 8.88%
found: C 44.22, H 8.49%

Silver Salt of Monomethyl-d_3 *Succinate (10).* — To a solution of the monomethyl ester *9* (1.36 g, 10.0 mmol) in redistilled CO_2-free water (10 ml), analytically pure sodium hydrogencarbonate (1.06 g, 10.0 mmol) was gradually added. The obtained solution was passed through a fluted filter which was subsequently rinsed with three 3-ml portions of water. Under vigorous stirring of combined filtrate and rinsings, a solution of silver nitrate (1.70 g, 10.0 mmol) in water (10 ml) was gradually added, which resulted in precipitation of *10*. The precipitate was collected on a filter and washed, first with water, then with methanol, and finally with ether (taking three portions of 5 ml of each washing liquid). After drying under reduced pressure, 1.79 g (74.8%) of *10* was obtained in an analytically pure form, m. p. 230—235 °C (dec.).

Anal. $C_5H_4D_3O_4$ (241.995) calc'd.: C 24.82, H 4.17%
found: C 24.67, H 4.02%

7-Chloro-1,3-dihydro-1-methyl-3-(methyl-d_3 *succinyl)oxy-5-phenyl-1,4-benzodiazepin-2-one (6).* — A solution of 3,7-dichloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepine-2-one (1.85 g, 5.81 mmol; synthesised as in ref. 28) was prepared with dry benzene (25 ml) and cooled in an ice bath with magnetic stirring, while gradually adding 1.29 g (5.35 mmol) of the silver salt *10*. Stirring was continued at room temperature for 22 h, carefully protecting the mixture from light and moisture. The precipitate formed at the end of this period was filtered off with suction using cellite as a filter-aid. The filtrate was evaporated in vacuo, and the oily residue was transferred to a chomatographic column (150 ml of silica gel). Elution was carried out with methylene chloride-acetone (95/5), and 10-ml fractions were collected. Crude *6*, 1.79 g (76%), was obtained from fractions 39—76. The later fractions 101—142 yielded 0.195 g of a side-product, 3-hydroxy-1,4-benzodiazepin-2-one.After recrystallizing the main product from methylene chloride-acetone (95/5), pure *6* was obtained, m. p. 63—65 °C. NMR ($CDCl_3$), ppm: 2.72 (t, J = 4.2 Hz, 2H), 3.49 (s, 3H), 5.99 (s, 1H), 7.2—7.8 (m, 8H). Ir (KBr) cm^{-1}: 1740, 1700, 1610, 1480, 1166, 830, 690.

Anal. $C_{21}H_{16}D_3ClN_2O_5$ (417.87) calc'd.: C 60.36, H 5.31, N 6.70%
found: C 60.53, H 5.47, N 7.59%

7-Chloro-1,3-dihydro-3-(methyl-d_3 succinyl)oxy-5-phenyl-1,4-benzodiazepin-2-one (*5*). — The procedure described in preparation of *6* was applied to 3,7-dichloro-1,3-dihydro-5-phenyl-1,4-benzodiazepin-2-one[26] (1.63 g, 5.36 mmol) and to the silver salt *10* (2.13 g, 7.00 mmol) in dry benzene (30 ml). However, because of limited solubility of the dichloro derivative in benzene 48 h were required to achive a high yield of *5* (as found by TLC-monitoring, eluant methylene chloride-acetone 90/10). Separation by column chromatography (150 g of silica gel) using the same eluant and collecting 10-ml fractions gave 2.23 g (82%) of crude *5* from fractions 74—118. Recrystallization from cyclohexane yielded pure *5*, m. p. 86—88 °C. NMR ($CDCl_3$), ppm: 2.74 (t, J = = 4.8 Hz, 2H), 6.00 (s, 1H), 7.1—7.8 (m, 8H), 10.1 (s, 1H).

Anal. $C_{20}H_{14}D_3ClN_2O_5$ (403.84) calc'd.: C 59.49, H 4.99, N 6.93%
found: C 59.51, H 4.75, N 7.29%

7-Chloro-1,3-dihydro-3-(methylsuccinyl)oxo-5-phenyl-1,4-benzodiazepin-2-one (*4*). — To prepare *4*, 3,7-dichloro-1,3-dihydro-5-phenyl-1,4-benzodiazepin-2-one[28] (3.04 g, 10 mmol) was reacted with silver salt of monomethyl succinate (2.65 g, 11 mmol) which was prepared by the same procedure as the trideuterated analogue *10* [m. p. of $C_5H_7AgO_4$: 242—246 °C (dec.)]. After carrying out the steps described in preparation of *5*, 3.4 g (80% of crude *4* was obtained which, on recrystallization from chloroform-diisopropyl ether, gave a pure product melting at 61—62 °C. NMR ($CDCl_3$), ppm: 2.72 (t, J = 4.2 Hz, 2H), 2.93 (t, J = 4.2 Hz, 2H), 3.68 (s, 3H), 5.94 (s, 1H), 7.1—7.8 (m, 8H), 10.2 (broad s, 1H).

Anal. $C_{21}H_{19}ClN_2O_5$ (424.85) calc'd.: C 59.37, H 4.51, N 8.34%
found: C 59.66, H 4.38, N 8.07%

Methyl 6-Chloro-1,2-dihydro-4-phenylquinazoline-2-carboxylate (*11*). — Compound *1* (1.0 g, 3.32 mmol) was dissolved in 5% methanolic hydrogen chloride (20 ml). The solution was heated to 40 °C and maintained at this temperature for 4 h. The solvent was than evaporated in vacuo leaving a red crystalline material. This residue was slurried in satd. sodium hydrogencarbonate, and extracted with ether (3 × 20 ml). The ethereal extract was dried (Na_2SO_4), freed of solvent by evaporation, and the residual material was recrystallized from ether-cyclohexane to give the pure product. After drying over P_2O_5 under reduced pressure (0.01 mm Hg) and careful protection from light (otherwise discoloration to intense red-brown occurs) the m. p. was 106—107 °C. NMR ($CDCl_3$), ppm: 3.82 (s, 3H), 4.89 (broad s, 1H), 5.47 (s, 1H), 6.66 (dd, J = 8.0 and 2.0 Hz, respectively, 1H), 7.0—7.7 (m, 7H). Ir (KBr), cm^{-1}: 3380, 2960, 1717, 1620, 1600, 1580, 1565, 1470, 1330, 895, 825, 811, 700.

Anal. $C_{16}H_{13}ClN_2O_2$ (300.71) calc'd: C 63.89, H 4.35, N 9.32%
found: C 63.61, H 4.09, N 9.17%

Methyl 6-chloro-4-phenylquinazoline-2-carboxylate (*12*). — To a solution of *11* (0.55 g, 1.83 mmol) in methanol (10 ml) 0.1 g of 10% Pd/C catalyst was added, and magnetic stirring was started. A stream of air was bubbled through the stirred solution during 4 h. At the end of this period the catalyst was removed by filtration, and the solvent by evaporation. The residual solid was recrystallized from ether-light petroleum to give 0.46 g (83.5%) of pure *12*, m. p. 132—134 °C. NMR ($CDCl_3$), ppm: 4.12 (s, 3H), 7.6—8.3 (m, 8H).

Anal. $C_{16}H_{11}ClN_2O_2$ (298.69) calc'd.: C 64.33, H 3.71, N 9.38%
found: C 64.41, H 3.59, N 9.09%

Pure *12* (0.2 g) was hydrolysed in 10% methanolic potassium hydroxide (5 ml) one hour at room temperature. The mixture was then neutralised with aqueous sodium acetate, and part of the solvent was evaporated. The remaining solution was extracted with ether (3 × 10 ml), and crude 6-chloro-4-phenylquinazoline-2-carboxylic acid (*13*) was obtained from the extract. Recrystallization from ether gave a purified product. m. p. 210—211 °C in good agreement with the literature[29] value 212.5—213.5 °C.

Kinetics

Polarimetry. — Racemisation rates were measured by weighing (50.0 ± 0.1)-mg samples of (+)-*1* ($[\alpha]_D = +197^0$, c = 0.80 in methanol) into 5.0 ml volumetric flasks, filling up to mark with methanolic hydrogen chloride and mixing to completely dissolve the sample. The time count was begun from this point on, but the follow-up of rotation values was started 5—6 min later, after the clear solution had been transferred to a 1-dm double-walled thermostated cell placed in the polarimeter. Minimum of 40 points has been used for rate calculations.

NMR spectrometry. — To measure rates of H/D exchange, racemic *1*, *2* and *3* were dissolved in methanolic-d_4 hydrogen chloride (DCl contents determined by automatic microtitration) and transfered immediately to the NMR tube. The time course of exchange was followed up at 1.5 to 2-min intervals integrating relevant NMR peaks. The follow-up was extended over 5—7 half-times, and minimum of 20 points has been obtained.

Side-reactions, as detected by TLC of samples of reaction mixtures taken at intervals, were only taken into account when at least 10% of starting material was diverted into a side-product.

Calculations of pseudo-first order rate constants, and of thermodynamic magnitudes, were carried out by computer using a non-linear least-squares program based on a program published in the Los Alamos Scientific Laboratory Report LA 2367 and its Addenda.

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SAŽETAK

Hiralni 1,4-benzodiazepin. X. Dalja istraživanja konfiguracione stabilnosti hiralnog centra C(3)

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Za različite na C(3) hiralne 1,4-benzodiazepin-2-one određene su brzina racemizacije (K_α- za C(3)-OCH_3 derivat (+)—*1*), brzina degenerirane nukleofilne zamjene (k_e- za rac. *1* i rac. *2*), te brzina solvoliza (k_s- za C(3)-hemisukcinil-derivat *4*). Ova istraživanja su pokazala; (*a*) retenciju konfiguracije tokom metanolize spoja (+)—*3*, (*b*) polaganu racemizaciju (+)—*1* tokom solvolitske degenerirane supstitucije ($k_e/k_\alpha \sim 4$), (*c*) da retenciju ne uzrokuje S_N1-reakcija, moguća intramolekularnim premještanjem metoksi skupine unutar intermedijera *4*—*6*, (*d*) slijedeće termodinamske parametre za racemizaciju (+)—*1* (između 20—40 °C); $\Delta H^{\neq} = 18.0 \pm 0.8$ kcal/mol, $\Delta S^{\neq} = -7.2 \pm 2.5$ e. u. Dana je mehanistička shema koja obuhvaća sve eksperimentalne rezultate. Ukratko se diskutira o mogućoj vezi između elektrocikličke ravnoteže, pretpostavljene za N(4)-protonirane 1,4-benzodiazepine, kao zajedničke osobine više sličnih struktura i mehanizma biološkog djelovanja na centralni nervni sustav.

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