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CHIRAL 1,4-BENZODIAZEPINES—XI[1]

KINETICS OF DEGENERATE NUCLEOPHILIC EXCHANGE OF C(3)-HYDROXY GROUP

V. Šunjić,* M. Oklobdžija, A. Lisini,[2] A. Sega and F. Kajfež
Department of Biomedical and Biochemical Research, CRC, Chemical Research Company, 33048 San Giovanni al Natisone (UD), Italy

and

D. Srzić and L. Klasinc
"Rugjer Bošković" Institute, P.O. Box 1016, 41001 Zagreb, Croatia, Yugoslavia

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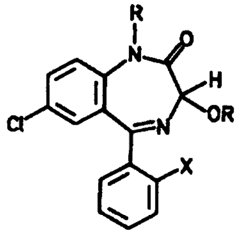
Abstract—The rate for degenerate nucleophilic exchange (k_e) of the C(3)–OH group in the racemic compound 1 was determined in DMSO/$H_2{}^{18}O$ using mass spectrometry. Epimerization rates for diastereomers 15 and 16 were determined by polarimetry (k_{ep}) and NMR spectroscopy (k_{r-c}—for ring–chain tautomery). The ratio $k_e/k_{ep} \sim 3.5$ at 35° is close to that obtained for degenerate nucleophilic exchange of the C(3)–OMe group in the compound 1a ($k_e/k_a \sim 4$, Refs. [3, 4]). These data confirm the C(3)–OH substituted 1,4-benzodiazepin-2-ones lose the configurational identity of the C(3) chiral centre by both direct nucleophilic substitution of the OH group, and ring–chain tautomery processes.

The synthesis of the diastereomeric compounds 15 and 16, and their chromatographic separation is described.

In our earlier papers in this series[1,3,4] we discussed the configurational stability of the chiral centre in some C(3)-methoxy and t-amino substituted benzodiazepines. Here we describe further investigations, on C(3)-hydroxy substituted benzodiazepine, i.e. on derivatives which possess pharmacologically the most important substituent on the C(3)-atom.[5] These compounds have currently proved to be the most important pharmacodynamics in the field of central nervous system (CNS) disorders,[5] and they are represented by temazepam, oxazepam and lorazepam (WHO names for the compounds 1–3).

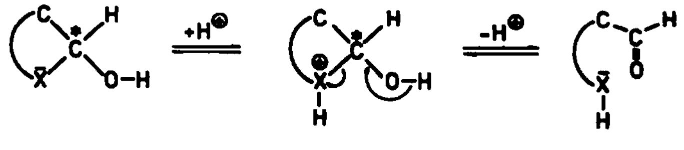
It was ascertained that the C(3)-methoxy derivative 1a undergoes degenerate nucleophilic exchange in acid methanolic solution, and mechanistic proposals for this process were offered.[1,4] For the C(3)-hydroxy derivatives 1–3, ring–chain tautomery is another possible mechanism for their racemisation. Moreover, degenerate nucleophilic solvolysis of the OH group could be diminished because of its lower nucleofugic aptitude. Ring–chain tautomery within C(3)-hydroxy-1,4-benzodiazepines could be regarded as a special case of the equilibrium inherent to the heterocyclic systems, as generally represented in Scheme 1.



	R	R_1	X
1	CH_3	H	H
1a	CH_3	CH_3	H
2	H	H	H
3	CH_3	H	Cl

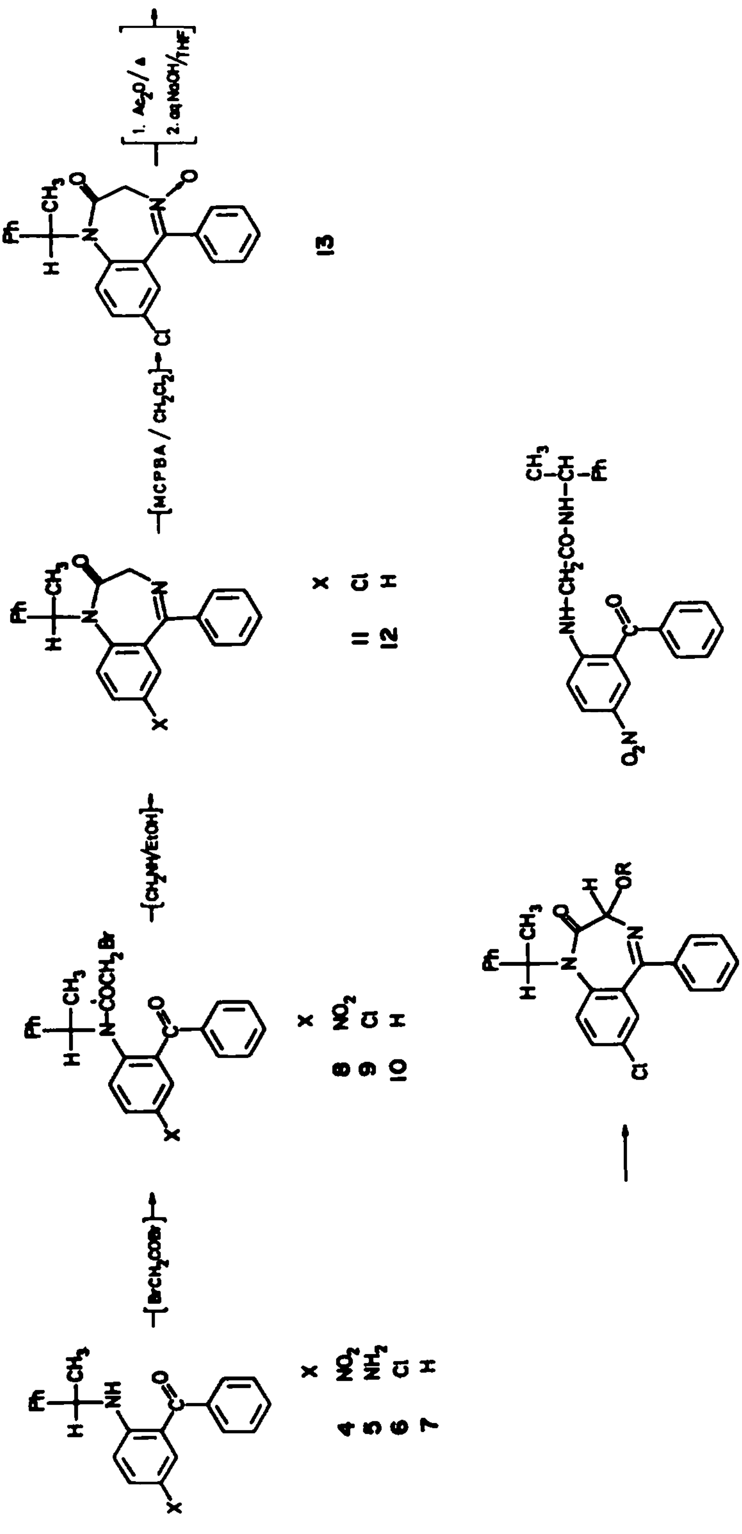
RESULTS

Synthetic part. To perform all envisaged kinetic measurements the racemic compound 1, and diastereomers 15 and 16 were required. Racemic 1 was used for mass spectrometric rate determination of exchange in ^{18}O labelled water, and no stereochemical information of



X = O, =N, NH, S

Scheme 1.



BrCH$_2$COBr
CH$_3$NH$_2$/EtOH
MCPBA / CH$_2$Cl$_2$
1. Ac$_2$O/Δ
2. aq NaOH/THF
X
4 NO$_2$
5 NH$_2$
6 Cl
7 H
X
8 NO$_2$
9 Cl
10 H
X
11 Cl
12 H
13
R
14,14A COCH$_3$
15 H
16 H
17

Scheme 2.

this experiment could be expected. Determination of the epimerisation rate for diastereomers 15 and 16, however, offers the possibility to evaluate the retention vs inversion ratio during exchange, as well as participation of the ring–chain tautomery in the over-all process.

The first, and defined (*S*) chiral centre in the diastereomeric 1,4-benzodiazepin-2-ones was introduced by incorporation of the (*S*)-(−)-α-phenylethylamine (PEA) moiety according to Scheme 2.

Compound 4 was prepared from 2-chloro-5-nitrobenzophenone in 72% yield, but its conversion into 6, via diazonium salts, rendered appreciable difficulties, so that only 30% of 6, beside 22% of dehalogenated 7 was separated after excessive chromatographic purification. Attempts to prepare the 7-nitro-analogue of 11, which was suspected to give on subsequent hydrogenation, diazotation and halogenation compound 11, failed, since intermediary compound 8 gave on heating in ethanol solution of hexamine only 17, i.e. the product of the Smiles rearrangement[6] instead of the expected 7-nitro-1,4-benzodiazepin-2-one. This rearrangement was repeatedly observed in the series of 2,5-disubstituted benzophenones.[7,8] 2-Fluoro-5-chlorobenzophenone, however, was successfully used as the starting material, since it afforded on condensation with (−)-PEA in HMPTA (hexamethyl phosphoric acid triamide) the compound 6 in 74% yield, while its preparation from 2-fluoro-5-nitrobenzophenone, as described in literature,[9,10] proceeded without difficulties. Compound 6 was acylated into 9, cyclised with hexamine, and N-oxygenated according to described procedures.[11] Interesting stereochemical properties of the compounds 12, 13 and some others, as revealed from their NMR spectra, are discussed in the next part. After Polonovsky-type rearrangement[12] of 13 into 14/14A (this mixture of diastereomers was not separated), and hydrolysis, diastereomeric mixture of 15 and 16 was obtained in an approx ratio of 1:1. They could be separated on tlc, but on standing for long periods (days), any of the separated spots gave on eluation two new spots, thus indicating their slow epimerisation catalysed by silicagel. Using column chromatography, we were able to separate two diastereomers 15 and 16.

Stereochemical properties. NMR spectra of the compounds 8–16 offer the possibility for determining various stereoelectronic origins for rotational or inversional barriers. While in the compounds 8–10 one element of chirality is present, cyclic compounds 11–13 possess a second element of chirality, i.e. a plane containing four planar atoms of the 7-membered ring, and compounds 14–16 contain the third element of chirality, i.e. a second chiral centre on C(3). Thus, compounds 8–10 exhibited two doublets at δ values of 1.05–1.15 ppm, and 1.50–1.62 ppm, respectively, for the two nonequivalent Me groups. Obviously, three large substituents on the N atom give rise to the high sterical restriction to rotation. Actually, the spectral effects observed for 8–10 can be interpreted in two alternative ways, i.e. by restricted rotation about the N–CO bond leading to geometrical isomerism, or by restriction to rotation about N–CHMePh bond giving slowly interconverting rotamers. However, in the same compounds methylenic protons give rise to only one AB system at 3.78–3.82 ppm. Doubling of the AB system is not observed, because two methylenic protons are either in the same magnetic environment in the two conformers, or more probably their rotation is fast relative to the NMR time-scale. Compounds 11 and 12 exhibited two doublets for the Me group, but doubled AB system of the methylenic groups within the ring could be noticed as well. Now chiral arrangement of the slow-inverting 7-membered ring rises magnetic nonequivalence of the methylene protons without two conformers. In the diastereomeric pairs 14/14A and 15/16 the third element of chirality, i.e. chiral centre C(3) is introduced. NMR spectra of these pairs exhibited two doublets for the Me group, and two singlets for the C(3)-proton. Compound 15 exhibited on separation only *one doublet* at 1.48 ppm for the Me group, and *one singlet* at 5.12 ppm for C(3)-proton (on addition of TFA-d$_1$ to eliminate its coupling with the OH group, however—see also Fig. 1). Diastereomer 16 possessed corresponding signals at 2.02 and 5.19 ppm.

Epimerisation 15⇌16, noticed on the silicagel plates, could easily be followed by the NMR, as indicated in Fig. 1.

This quantitive picture was quantitatively confirmed by the rate measurements as described in the next paragraph.

Kinetics of the C(3)–OH *exchange and epimerization*. The equilibrium shown in Scheme 3 was monitored in a solvent mixture DMSO/H$_2{}^{18}$O by mass spectrometry. Relative enhancement of M + 2 ion peak could be followed (Fig. 2).

It was found that the process obeys *pseudo*-first order kinetics (k$_e$) well, and is temperature dependent. Rele-

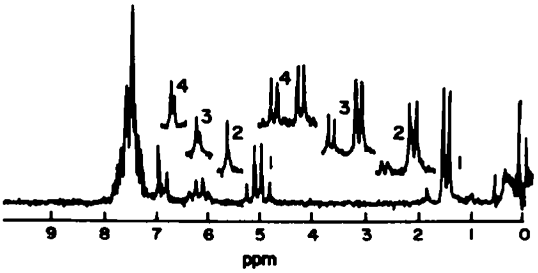
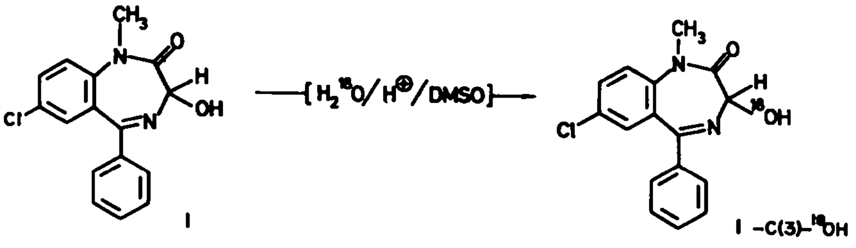


Fig. 1. The dependent part is the NMR spectra of 15 (10% soln in CDCl$_3$/TFA-d$_1$). (1) Spectrum of 15 in CDCl$_3$, (2) spectrum of 15 immediately after addition of a drop of TFA-d$_1$, (3) the same after 58 min, (4) the same after 202 min (equilibrium state).



Scheme 3.

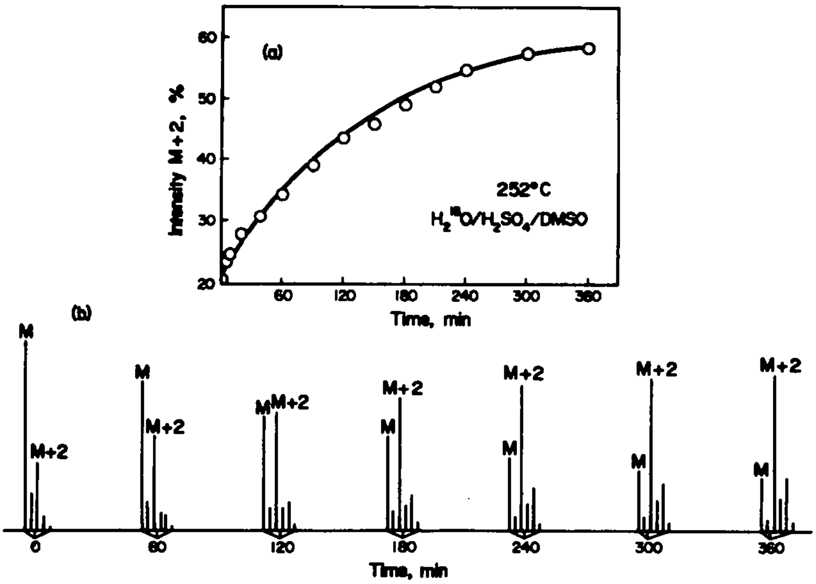


Fig. 2. (A) Time dependent intensity of M+2 ion for C(3)–OH→C(3)–^{18}OH exchange in 1. (B) Time dependent *m/e* intensities in the region 298–302 mass units.

vant kinetic and thermodynamic data are summarised in the Table 1.

In order to obtain further insight into the mechanism of configurational loss of the C(3)-chiral centre polarimetric measurements afforded highly accurate data for the ratio of epimerization (k_{ep}) of the compounds **15** and **16**. They are presented in Table 2.

Rather low values for activation parameters obtained for these processes, as indicated on the bottom of the Tables 1 and 2, revealed that N(4) protonated 3-hydroxy-1,4-benzodiazepin-2-ones are very prone to substitution and tautomerization. We hesitate to draw any mechanistic conclusion from these data.

Epimerisation of **15** and **16** was followed by NMR spectroscopy. Because of the vicinity of the signals for diastereotopic protons on C(3) accurate time-dependent integration was not possible. It was possible, however, for the two doublets of the Me groups in **15** and **16**, giving the following rates of ring–chain tautomery (k_{r-c}):

$$\mathbf{15} \ldots k_{r-c} = (1.09 \pm 0.05) \times 10^{-3}/s$$
$$\mathbf{16} \ldots k_{r-c} = (0.33 \pm 0.05) \times 10^{-3}/s$$

as determined in TFA-d_1/DMSO-d_6 (1:7) at 35±0.1°.

From the data for k_e and k_{ep} at 35.0° (Tables 1 and 2) the ratio $k_e/k_{ep} \sim 3.5$ could be calculated. It reveals one inversion of configuration per three to four epimerisation events, and is very close to the ratio $k_e/k_\alpha \sim 4$ found for degenerate exchange of the C(3)-OMe group.[3,4] The above relation between k_e and k_{ep} is entirely justified, although they are determined by two different kinetic methods, since the same solvent mixture was used,[13] no concentration dependence of the k_{ep} was observed (runs 11–14 in Table 2). In principle, from the three rate constants, k_e, k_{ep} and k_{r-c}, even inversion vs retention pathway of k_e could be calculated according to the following consideration: the total exchange rate determined by mass spectrometry (k_e) is a sum of the inversion part (k_{e-inv}) and retention part (k_{e-ret}). Epimerisation rate determined by polarimetry (k_{ep}) consists of k_{e-inv} part of nucleophilic exchange, and ring–chain epimerisation rate: thus, the following expressions could be written:

$$k_e = k_{e-inv} + k_{e-ret} \qquad k_{ep} = k_{e-inv} + k_{r-c}$$

hence;

$$k_{ep} = k_e - k_{e-ret} + k_{r-c} \qquad k_{e-ret} = k_{r-c} + k_e - k_{ep}.$$

Table 1. Rate constants k_e and thermodynamic parameters for exchange reaction 1→1 –C(3)–^{18}OH

Run no.	t /°C	$k_e \times 10^3$/s
1.	25.2 ± 0.1	0.95 ± 0.02
2.	35.0 ± 0.1	1.90 ± 0.02
3.	49.9 ± 0.1	7.57 ± 0.05
4.	59.8 ± 0.1	12.0 ± 0.1

$$\Delta H^{\ddagger} = 51.0 \pm 7.9 \text{ kJ mol}^{-1}$$
$$\Delta S^{\ddagger} = -113.8 \pm 23.4 \text{ J K}^{-1}\text{mol}^{-1}$$

Table 2. Rate constants k_{ep} and thermodynamic parameters for epimerization $15 \rightleftharpoons 16$

COMPOUND 15				COMPOUND 16			
Run no.	t/°C	C(mg/2ml)	$k_{ep} \times 10^3$/s	Run no.	t/°C	C(mg/2ml)	$k_{ep} \times 10^3$/s
1.	25	10.0	0.19 ± 0.002	15.	25	10.0	0.19 ± 0.003
2.	25	10.0	0.19 ± 0.002	16.	35	10.0	0.55 ± 0.002
3.	35	10.0	0.55 ± 0.005	17.	35	10.0	0.54 ± 0.002
4.	35	10.0	0.54 ± 0.002	18.	43	10.0	1.30 ± 0.002
5.	37	10.0	0.68 ± 0.002	19.	50	10.0	2.58 ± 0.02
6.	37	10.0	0.69 ± 0.003	20.	60	10.0	6.47 ± 0.02
7.	43	10.0	1.21 ± 0.001				
8.	50	10.0	1.55 ± 0.003				
9.	55	10.0	2.03 ± 0.02				
10.	60	10.0	3.97 ± 0.07				
11.	35	5.0	0.56 ± 0.002				
12.	35	20.0	0.56 ± 0.002				
13.	35	30.0	0.54 ± 0.005				
14.	35	40.0	0.55 ± 0.007				

$\Delta H^{\ddagger} = 64.9 \pm 4.2$ kJ mol^{-1}
$\Delta S^{\ddagger} = 40.6 \pm 13$ J K^{-1}mol^{-1}

$\Delta H^{\ddagger} = 80.3 \pm 0.4$ kJ mol^{-1}
$\Delta S^{\ddagger} = 10.9 \pm 1.7$ J K^{-1}mol^{-1}

There is a practical obstacle to the above considerations, however. The NMR determined rate, k_{r-c}, should have been obtained in *non-aqueous* solvent system, in order to exclude the substitution pathway, as it was the case in our experiments. The constants k_{ep} and k_{r-c} obtained in different solvent systems are however not comparable, any more. In fact, only for compound **16** reasonable value for k_{o-rot} (1.69×10^{-3}/s) turns out from the last equation, while for the other diastereomer **15** a non-realistic value (2.45×10^{-3}/s) emerges, i.e. higher than k_e itself. Different contributions of the k_{r-c} in the cumulative epimerisation process of the two diastereomeric carbinolamines should be expected.[14]

In conclusion it could be stated that the 3-hydroxy-1,4-benzodiazepin-2-ones belong to the rare heterocycles with the relatively stable carbinolamine function (also called hemiaminal or amino-hemiacetal), being in the fast equilibrium with its open aldehydic form. Although several natural compounds have recently been recognised to possess a stable amino-hemiacetal function,[17–19] this function is usually found to be rather unstable, and plays certain role only in the biosynthesis of alkaloids.[20,21] In the 3-hydroxy-1,4-benzodiazepin-2-ones the amino group is the part of an azomethyne moiety, and this is the structural feature that renders relative chemical stability to the cyclic form of these compounds. Processes of the loss of configurational identity of the C(3)-chiral centre we report in this paper definitely exclude *enantiomers* of C(3)-hydroxy-1,4-benzoidiazepin-2-ones as a possibly more interesting pharmacodynamic species in the treatment of the CNS disorders. The same process turns to be a reason for the optical inactivity of the isolated, although *in vivo* stereospecifically oxygenated C(3)-hydroxy-1,4-benzodiazepin-2-ones, as we already proposed in our recent metabolic study.[11]

EXPERIMENTAL

M.ps were determined on a Kofler microheating stage (Bŏetius) and are not corrected. IR spectra (KBr pellets) were obtained with a Perkin–Elmer M 297 spectrophotometer (absorptions in cm^{-1}—only strong bands are indicated). NMR spectra were run on a Perkin–Elmer R 12 instrument with TMS as an internal standard. Shifts are given in ppm values downfield from TMS. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. Tlc was performed on aluminium or glass plates precoated with Merck's silica gel 60F 254. Column chromatography was run over granular silica gel, 0.05–0.2 mm (Merck). Organic extracts were regularly dried over Na_2SO_4 and evaporated *in vacuo*.

2 - [α - (S) - *Phenylethylamino*-] - 5 - *nitrobenzophenone* (4)

2 - Chloro - 5 - nitrobenzophenone (100.0 g, 38.2 mmol), and α(−)-phenylethylamine (puriss., Fluka; 95.0 g, 78.4 mmol) were dissolved in HMPTA (150 ml), and heated under stirring for 4 hr at 100°. Thereafter about 130 ml of HMPT was distilled off *in vacuo*, the residual oil was slurried in water (800 ml) and extracted with CH_2Cl_2 (3 × 250 ml). The extracts were washed with water (3 × 400 ml) and dried, evaporated and residual oil crystallised from diisopropylether (150 ml), yielding 96 g (72%) of the product **4**, m.p. 70–74°, anal. sample melted at 72–74°. IR: 3280, 1630, 1535, 1500, 1330, 1260, 1120, 650 cm^{-1}. NMR ($CDCl_3$): 1.75 (d, 3 H), 4.75 (q, 1 H), 6.8–8.6 (m, 13 H), 9.8 (d, 1 H, NH). (Found: C, 72.86; H, 5.41; N, 8.03. $C_{21}H_{18}N_2O_3$ requires: C, 72.81; H, 5.24; N, 8.09%).

The same compound could be prepared in about 65% yield by heating the above reactants (1:2 mol) without solvent, in a sealed-tube, for 8 hr at 160°. The isolation of the products was performed as above.

2 - [α - (S) - *Phenylethylamino*-] - 5 - *aminobenzophenone* - *hydrochloride* (5)

To the compound **4** (30 g, 86.6 mmol) dissolved in glac AcOH (230 ml) a soln of $SnCl_2 \cdot H_2O$ (75 g) in a mixture of glac AcOH (250 ml) and 6 NHCl (100 ml) was added dropwise at ambient temp. during 1 hr. After stirring vigorously for 48 hr, ice water was added (1500 ml), and resulting suspension made alkaline with 40% NaOH aq. This slurry was extracted with EtOAc (3 × 400 ml), the organic extracts washed with water, dried (Na_2SO_4), and evaporated. The residual red oil was crystallised from diisopropylether (50 ml) to afford 21 g (76%) of pure **5**, m.p. 90–91°, $[\alpha]_D = +575°$ ($c = 0.5$ in $CHCl_3$). IR: 3440, 3360, 3320, 1615, 1570, 1515, 1230, 970, 815, 705 cm^{-1}. NMR ($CDCl_3$): 1.5 (d, 3 H), 3.05 (broad 2 H, NH_2), 4.3–4.9 (m, 1 H), 6.3–7.9 (m, 13 H), 8.55 (broad

1 H, NH). (Found: C, 79.40; H, 6.60; N, 8.90. $C_{21}H_{20}N_2O$ requires: C, 79.71; H, 6.37; N, 8.85%).

2 - [α - (S) - *Phenylethylamino*] - 5 - *chlorobenzophenone* (6)

Method A. Compound 5 (12.0 g, 3.82 mmol) was slurried in 3 N HCl (80 ml) at 0°, and a soln of $NaNO_2$ (2.8 g, 3.87 mmol) in water (60 ml) was added under vigorous stirring, and maintaining the temp. below 5°. After 20 min stirring between 0 and 5° the resulting diazonium salt soln was poured into a soln of CuCl (7.8 g, 7.9 mmol) in 6 N HCl (80 ml). The mixture was stirred 1 hr at 0°, then 20 min at 60°. To the resulting slurry water (200 ml) was added, then pH adjusted to 9 with conc. aq. ammonia and extracted with CH_2Cl_2 (3 × 200 ml). The combined extracts were dried, evaporated and residual oily mass applied to a silica gel (450 g) column. On eluation with benzene the first fraction afforded 2.8 g of pure 6, which on crystallisation from diisopropylether melted at 122–123°. $[\alpha]_D = +423.7^\circ$ ($c = 1.11$ in $CHCl_3$). IR: 3320, 1610, 1570, 1505, 1445, 1405, 1240, 1205, 815, 745, 700 cm^{-1}. NMR ($CDCl_3$): 1.56 (d, 3 H), 4.56 (q, 1 H), 6.42 (d, 1 H), 7.0–7.7 (m, 12 H), 8.9 (d, 1 H–NH). (C, 75.33; H, 5.47; N, 4.42: $C_{21}H_{18}ClNO$ requires: C, 75.11; H, 5.40; N, 4.17%.

The other fractions contained 3 g of the mixture which was rechromatographed to give 0.7 g of pure 6 (total yield 30%) and 2.3 g of 7 (22%), m.p. 103–104°. $[\alpha]_D = +498$ ($c = 2.02$ in $CHCl_3$). IR: 3330, 1625, 1585, 1520, 1460, 1265, 758, 705. (C, 83.76; H, 6.58; N, 4.80. $C_{21}H_{19}NO$ requires: C, 83.68; H, 6.35; N, 4.65%).

Method B. 2 - Fluoro - 5 - chlorobenzophenone (14.0 g, 5.96 mmol, prepared from 2 - fluoro - 5 - nitrobenzophenone according to the lit.[9,10]), and α-(−)-PEA (15.2 g, 5.96 mmol) were dissolved in HMPTA (100 ml) and heated under stirring for 8 hr at 120°. The mixture was cooled, poured in ice-water (400 ml), product extracted with ether (3 × 150 ml), and ethereal extracts washed with water (3 × 200 ml). After drying and evaporation residual oil was crystallised from MeOH to afford 15.8 g (73.6%) of 6; m.p. 122–123°.

2 - [α - (S) - *Phenylethyl* - N - *bromoacetylamino*] - 5 - *nitrobenzophenone* (8)

Compound 4 (8.0 g, 2.38 mmol) was dissolved in benzene (100 ml), and maintaining the temp. below 10° bromoacetylbromide (4.0 g, 1.19 mmol) was added under stirring. The stirring was continued for 1 hr at ambient temp. and then 2 hr at 60°. Thereafter water (100 ml) was added, and after shorter stirring the layers separated. Organic layer was additionally washed with water (2 × 100 ml), dried and evaporated. On crystallisation from diisopropylether 9.5 g (85%) of 8 with m.p. 111–112° was obtained, IR: 1660, 1615, 1530, 1385, 1350, 710. NMR ($CDCl_3$):1.15 and 1.62 (two d, 3 H, CH_3), 3.78 (2 H, dd, CH_2), 6.15 (1 H, m, CH), 6.8–8.4 (13 H, m). (Found: C, 59.28; H, 4.40; N, 5.94. $C_{23}H_{19}BrN_2O_4$ requires: C, 59.13; H, 4.10; N, 5.99%).

2 - [N - (β - *Phenylethylamido*) - *acetylamino*] - 5 - *nitrobenzophenone* (17)

Compound 8 (13.5 g, 2.89 mmol) and hexamine (13 g), were heated in abs EtOH (150 ml) for 8 hr under reflux. EtOH was evaporated to dryness, the residue slurried in water (20 ml), filtered and repeatedly washed with water. Crude 17 thus obtained was crystallised from EtOH affording 6.0 g (52%) of pure 17, pale-yellow crystals with m.p. 228–229°. IR: 3330, 3270, 1660, 1640, 1620, 1340, 1245. NMR (DMF-d_7): 1.48 (d, 3 H), 4.27 (d, 2 H, a part of AB system), 5.12 (q, 1 H), 6.92 (d, 1 H), 7.1–8.6 (m, 12 H), 9.85 (t, 1 H–NHCO). (C, 68.70; H, 6.38; N, 10.20. $C_{23}H_{21}N_3O_4$ requires: C, 68.47; H, 5.25; N, 10.42%).

2 - [α - (S) - *Phenylethyl* - N - *bromoacetylamino*] - 5 - *chlorobenzophenone* (9)

Starting from 6 (7.0 g, 2.08 mmol), dissolved in benzene (120 ml), and bromoacetylbromide (7.5 g, 3.75 mmol) compound 10 was obtained in 95% yield (8.5 g), following the same procedure as described for 8. After crystallisation from diisopropylether it has m.p. 118–119°. $[\alpha]_D = +75.2$ ($c = 1$ in $CHCl_3$). IR: 1680, 1660, 1595, 1440, 1415, 1385, 1320, 1280, 1205, 915, 695. NMR ($CDCl_3$): 1.05 and 1.50 (3 H, two d, CH_3), 3.82 (2 H, dd, CH_2), 5.96 (1 H, q, CH), 6.8–8.0 (13 H, m). (C, 60.27; H, 4.07; N, 3.34. $C_{23}H_{19}ClBrNO_2$ requires: C, 60.47; H, 4.19; N, 3.06%).

2 - [α - (S) - *Phenylethyl* - N - *bromoacetylamino*] - *benzophenone* (10)

Compound 7 (1.0 g, 2.3 mmol) was α-bromoacetylated under the same conditions as described for 8, but performing the reaction first 0.5 hr at ambient temp., then on heating 1 hr under reflux. Crude product was crystallised from EtOH to afford 1.2 g (85%) of pure 10, m.p. 116–117°. $[\alpha]_D = +55.5$ ($c = 1$ in $CHCl_3$). IR: 1680, 1665, 1595, 1450, 1381, 1325, 1290, 700 cm^{-1}. NMR ($CDCl_3$): 1.12 and 1.59 (3 H, two d, CH_3), 3.80 (2 H, dd, CH_2), 5.96 (1 H, q, CH), 6.4–8.1 (14 H, m). (C, 65.26; H, 5.03; N, 3.50. $C_{23}H_{20}BrNO_2$ requires: C, 65.40; H, 4.77; N, 3.31%).

1 - [α - (S) - *Phenylethyl*] - 5 - *phenyl* - 7 - *chloro* - 1,3 - *dihydro* - 2 H - 1,4 - *benzodiazepin* - 2 - *one* (11)

Compound 9 (8.0 g, 1.75 mmol), hexamine (8.0 g), and ammonium chloride (0.8 g) in abs EtOH (120 ml) were heated under reflux for 18 hr. The solvent was evaporated to dryness, the residue slurried in water (200 ml) and extracted with EtOAc (3 × 150 ml). After drying and evaporation crude 11 was crystallised from diisopropylether. On prolonged chilling on ice (sometimes days were required) it crystallised in prysmatic crystals (5.5 g, 92%) with m.p. 131–132°. $[\alpha]_D = -9.5$ ($c = 2.03$ in $CHCl_3$). IR: 1670, 1600, 1475, 1440, 1400, 1320, 735, 695. NMR ($CDCl_3$): 1.42 and 1.98 (3 H, two d, CH_3), 3.88 and 4.94, then 3.82 and 4.88 (2 H, two doubled dd, two AB systems, CH_2), 6.06 (1 H, m, CH), 6.7–7.8 (13 H, m). (C, 73.72; H, 5.25; N, 7.58. $C_{23}H_{19}ClN_2O$ requires: C, 73.69; H, 5.11; N, 7.47%).

1 - [α - (S) - *Phenylethyl*] - 5 - *phenyl* - 1,3 - *dihydro* - 2H - 1,4 - *benzodiazepin* - 2 - *one* (12)

Starting from 10 (1.90 g, 4.16 mmol) compound 12 has been prepared in 64% yield following the same method as described for 11, m.p. 143–144° (from diisopropylether). IR: 1660, 1600, 1565, 1480, 1442, 1380, 1340, 1320, 1245, 1190, 700 cm^{-1}. (Found: C, 81.02; H, 5.56; N, 8.41. $C_{23}H_{20}N_2O$ requires: C, 81.15; H, 5.92; N, 8.23%).

7 - *Chloro* - 1 - [α - (S) - *phenylethyl*] - 5 - *phenyl* - 1,3 - *dihydro* - 2 H - 1,4 - *benzodiazepin* - 2 - *one* - 4 - *oxide* (13)

Compound 11 (4.2 g, 11.2 mmol) was dissolved in CH_2Cl_2 (80 ml), and a soln of *m*-chlorperbenzoic acid (MCPBA) (6.0 g, 34.7 mmol) in CH_2Cl_2 was added, dropwise during 40 min, under stirring and at ambient temp. After additional 2 hr stirring at ambient temp. the reaction was poured in water (200 ml), organic layer separated and washed with 5% $NaHCO_3$aq (2 × 150 ml), then with water (200 ml). After drying (Na_2SO_4) and evaporation residual oil was purified on a silicagel (200 g) column using benzene–ether (1:1) as eluant, yielding 4.1 g (93%) of pure 13, which was crystallised from diisopropylether-light petroleum, m.p. 111–112°. IR: (KBr): 1680, 1575, 1485, 1415, 1290, 1230, 745, 695 cm^{-1}. NMR ($CDCl_3$): 1.15 and 1.45 (3 H, two d, CH_3), 4.5–4.9 (2 H, m), 5.7–6.4 (1 H, m), 6.7–8.2 (13 H, m). In the NMR spectrum of this compound additional signals were regularly present at 1.45 and 1.57 ppm (two d), which, together with the appearance of unresolvable multiplets for CH_2, and CH group, indicate a presence of the rearranged compound 4,5 - oxazirino - benzodiazepin - 2 - one. It is well known that N-oxydes of 1,4 - benzodiazepines easy rearrange into corresponding oxazirinoderivatives.[23] (C, 70.38; H, 5.21; N, 7.02. $C_{23}H_{19}ClN_2O_2$ requires: C, 70.67; H, 4.90; N, 7.17%).

7 - *Chloro* - 1 - [α - (S) - *phenylethyl*] - 5 - *phenyl* - 3 - *acetoxy* - 1,3 - *dihydro* - 2H - 1,4 - *benzodiazepin* - 2 - *ones* (14, 14A)

Compound 13 (6.0 g, 15.3 mmol) was dissolved in acetanhydride (90 ml), and stirred for 3 hr at 80°. After evaporation to dryness, residue was crystallised from diisopropylether to afford 6.2 g (93%) of the diastereomeric mixture which melted at 207–208°. $[\alpha]_D = -39.5$ ($c = 1$ in $CHCl_3$). IR: 1740, 1695, 1615, 1480, 1415, 1330, 1240, 1095, 705. NMR ($CDCl_3$): 1.40 and 1.90 (two d, CH_3), 2.30 (s, 3 H, $COCH_3$), 5.5–6.5 (m, 2 H–C(3)H and N(1)–CHMePh), 6.7–8.0 (13 H, m). (C, 69.13; H, 5.01; N, 6.22. $C_{25}H_{21}ClN_2O_3$ requires: C, 69.36; H, 4.89; N, 6.47%).

7 - *Chloro* - 1 - [*α* - (S) - *phenylethyl*] - 5 - *phenyl* - 3 - *hydroxy* - 1,3 - *dihydro* - 2H - 1,4 - *benzodiazepin* - 2 - *ones* (15, 16)

Diastereomeric mixture 14, 14A (7.3 g, 16.9 mmol) was dissolved in THF (100 ml) and under stirring at room temp. 2.5% NaOH aq (30 ml) was added, dropwise. After 4.5 hr stirring the mixture was diluted with water (300 ml) and extracted with CH_2Cl_2(3×150 ml). After washing with water (2×200 ml), drying and evaporation residual, pale-yellow oil was chromatographed on silicagel (450 g) column using diisopropylether as the eluant. Two diastereomers 15 and 16 were separated, using LKB M 7000 automatic fraction collector, as follows: fractions 30–70 (10 ml per fraction) contained 1.5 g of pure 15, which on recrystallisation from MeOH (5.0 ml) had m.p. 149–150°. Fractions 71–100 contained 1.6 g of the mixture 15/16, and fractions 101–152 contained 0.85 g of pure 16 which on recrystallisation from MeOH-diisopropylether had m.p. 149–150°. Compound 15: $[\alpha]_D^{22} = +136.4$ ($c = 2.05$ in $CHCl_3$). IR: 3490, 1680, 1608, 1480, 1402, 1320, 1220, 1115, 1010, 705 cm^{-1}. (C, 70.88; H 5.03; N, 7.28. $C_{23}H_{19}ClN_2O_2$ requires: C, 70.67; H, 4.90; N, 7.17). For the NMR spectrum see Fig. 2.

Compound 16: $[\alpha]_D^{22} = -243.8$ ($c = 1.0$ in $CHCl_3$), m.p. 136–137°. NMR ($CDCl_3$): 2.06 (d, 3 H), 5.12 (d, 1 H, OH), 5.19 (d, 1 H, C(3)–H-on addn. of TFA-d_1, turns into s), 6.08 (q, 1 H), 6.88 (d, 1 H C(9)–H on the benzene ring), 7.1–7.9 (m, 12 H). (C, 70.39: H, 4.68; N, 7.31. $C_{23}H_{19}ClN_2O_2$ requires: C, 70.67; H, 4.90; N, 7.17%).

Kinetics

Mass spectrometry. Compound 1 (100 mg) was dissolved in a mixture of DMSO (1.4 ml) and $H_2{}^{18}O$–H_2SO_4 (26.5% H_2SO_4, 0.20 ml). The resulting soln was thermostated in the septum stopped probe tube (Colora Ultratermostat typ NB) and 0.2 ml samples were taken off at regular time intervals using 0.5 ml syringe. Samples were quenched by adding to a mixture of 5% NaOAc aq (1 ml) and $CHCl_3$ (1 ml). After brief shaking layers were left for about 0.5 hr to separate, and bottom organic layer was taken off by a pipette. It was evaporated to dryness, and residue was additionally dried at 0.02 mm Hg over P_2O_5 for 3 hr. Samples thus obtained were directly injected into mass spectrometer.

Mass spectrometric measurements of $^{18}OH/OH$ exchange rates at C(3) have been performed by determination the relative enhancement of the $M+2$ ion peak. The intensity of the $M+2$ ion was calculated in percentage of the sum of ion currents of the $M-1$ to $M+2$ ions.

All mass spectrometric measurements were performed on a Varian MAT-CH 7 instrument. The samples were introduced directly into the ion source via a heated direct insertion probe. Operating conditions were: electron energy 70 eV, ionising current 100 μA, ion acceleration voltage 3 kV, source pressure 10^{-6} Torr.

NMR spectrometry. Compound 15 (50.0 mg) was dissolved in DMSO-d_6 and TFA-d_1 (7:1, vol/vol). Integration of the signals at 1.5 and 2.05 ppm was performed during 24 hr, at temp. $35 \pm 0.1°$.

Polarimetric measurements. They have been performed using Perkin–Elmer M 141 polarimeter equipped with a double-wall 1 dm cell. Thermostation of the cells has been performed using Colora Ultratermostat type NB. For temp. dependent rate measurements sanples of 10.0 mg of 15 were dissolved in 2.0 ml calibrated flasks, while for the concentration dependent rate measurements samples of 5.0, 10.0, 20.0, 30.0 and 40.0 mg/2 ml were used. Tlc control of the solns after the kinetic runs revealed pure chemical transformations 15⇌16, no spots of the solvolytic side-product were indicated.

Calculations. All kinetics were calculated using a non-linear least-squares program as aready described.[2,3]

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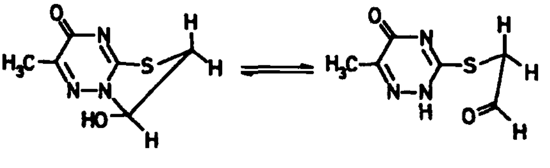
[14] Recently Toth *et al.*[15] reported a nice NMR study of ring–chain tautomery for the system 18⇌19, and proved that the ratio of the open-chain form enhanced at higher temperatures.



18 19

Hamada *et al.*[16] proposed ring fission of N-acylated-2-hydroxyquinolines and formation of an intermediate hemiacetal, during C(2) alkoxylation of these compounds. This is an additional case of the ring–chain equilibrium, now in the fused 6-membered ring.

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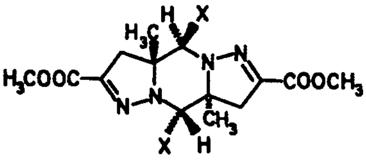
[21] Another stable tricyclic amino hemiacetal (**20a**) was recently described.[22]



	X
20a	OH
20b	OCH_3
20c	OCH_2CF_3 etc.

The authors found that substitution of the OH groups in **20a** proceeds under complete *retention of configuration*, as confirmed by X-ray diffractometric analysis of **20b**. The authors offer no mechanistic explanation of this stereochemical outcome, yet it is closely related to our finding[1,4] of high degree of retention during nucleophilic exchange of the C(3)-methoxy group in some 1,4-benzo-diazepin-2-ones.

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