

CCA-844

YU ISSN 0011-1643

547.892

Original Scientific Paper

Chiral 1,4-Benzodiazepines. VIII¹. Concerning the Rate of H/D Exchange and Optical Stability of the Chiral Centre C(3).

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Various chiral substituted 1,4-benzodiazepin-2-ones with 3-acyloxy (general formula I), 3-hydroxy- and 3-alkoxy (general formula II), 3-alkyl (general formula III) and 3-quaternary ammonium (general formula IV) groups as substituents were subjected to C(3)-H-D exchange rate measurements in order to obtain information on the optical stability of the chiral centre and on the mechanism of racemization. Only type IV compounds (IVa—j) exhibited H/D exchange, but acid catalyzed racemization took place in type I and II compounds, indicating some other mechanisms in this process. Type III compounds as free bases (IIIa—c), N⁴-protonated acids, or N⁴-oxides (III, e; f) underwent no H/D exchange and are optically stable as well. In cases where deprotonation-reprotonation mechanism of racemization can be excluded two other mechanisms are discussed, *i. e.* acid-catalyzed ring-chain tautomerism and identity substitution with alkoxide ion.

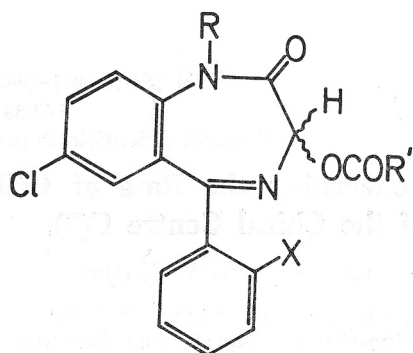
INTRODUCTION

In our recent paper² unsuccessful attempts at resolution of racemic 3-hydroxy derivatives of 7-chloro-5-phenyl-1,4-benzodiazepin-2-ones (IIa and IIb) were described. Some pharmacological aspects of this work prompted us to further investigation of the chiral 1,4-benzodiazepines. In the mentioned paper it was proposed that racemization of the resolved diastereomeric esters Ia-c takes place by acid- or base-catalyzed proton exchange at the chiral centre during hydrolysis. In the present work we report our results on n.m.r. H/D exchange measurements and related investigations on various chiral 1,4-benzodiazepines which give insight into the mechanism of racemization, and information about their optical stability.

RESULTS AND DISCUSSION

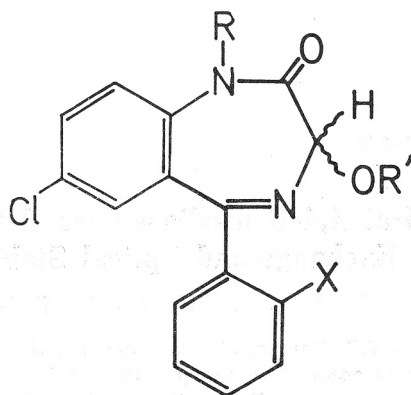
A. 3-Hydroxy-, alkoxy- and acyloxy-1,4-benzodiazepin-3-ones

N.m.r. measurements of H/D exchange rates at C(3) have been performed in the compounds Ia, a', Ic³, IIb, d, e, and f. Using methanol-*d*₄ with and without addition of 0.05 M sulfuric acid-*d*₂, no H/D exchange was obtained in any compound investigated. Experiments were performed at (35 ± 0.1) °C during 48 h, *i. e.* through a period about 10 times longer than that required for complete acid catalyzed methanolysis of compounds Ia and Ic.



Ia—d

	X	R	R'
a, a'	H	H	Camphoyl
b, b'	H	CH ₃	Camphoyl
c, c'	Cl	H	Camphoyl
d	H	H	Hemisuccinyl



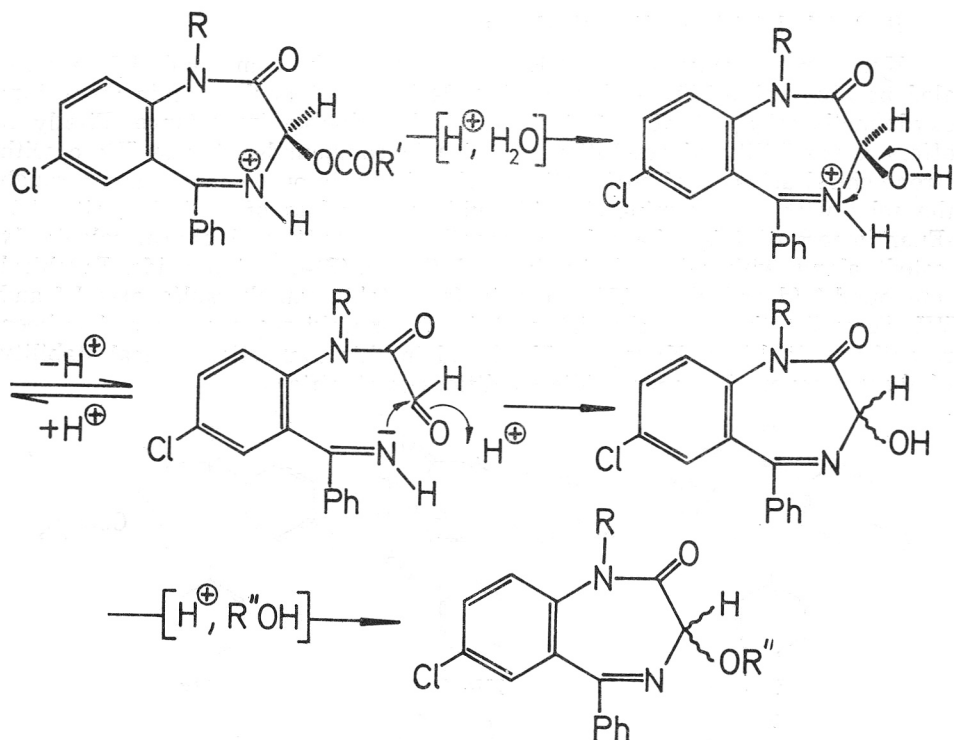
IIa—f

	X	R	R'
a	H	H	CH ₃
b	H	CH ₃	CH ₃
c	H	H	C ₂ H ₅
d	Cl	H	C ₂ H ₅
e	H	H	H
f	H	CH ₃	H

Parallel racemization rate measurements were performed on the optically active (+)-IIId, prepared according to the described procedure⁴. The first-order rate profiles were obtained in 10% ethanolic hydrogen chloride ($k_{\text{obs}} = 3.94 \times 10^{-3} \text{ min}^{-1}$) and in the mixture of 10% ethanolic hydrogen chloride-water (4:1, $k_{\text{obs}} = 9.72 \times 10^{-3} \text{ min}^{-1}$) as well. These results exclude deprotonation-reprotonation on C(3) as a mechanism of racemization, because in such a case H/D exchange rate should correspond to the racemization rate measured polarimetrically⁵. The formation of racemic compounds IIa and IIb during acid catalyzed solvolysis of optically pure diastereomers Ia and Ib was observed earlier². A seemingly attractive explanation of all these findings is that formation of the carbonium ion on the chiral centre C(3), followed by nonstereospecific attack of the solvent, lead to racemization. Two objections can be put forward against such a racemization mechanism. The first, 1,4-benzodiazepines are N(4) protonated under acidic conditions employed, so that ion derived by loss of RCOOH (or ROH) from such protonated species would be doubly positively charged. The second, solvolytic reactions on conformationally rigid, saturated carbo- or heterocycles exhibited high retention of configuration, even when a carbonium ion is an intermediate⁶⁻⁹. In fact, rigid conformation was recently found¹⁰ in a number of 3-substituted 1,4-benzodiazepin-2-ones. We have also repeatedly observed^{2,3} singlets at about 6.1 ppm for diastereotopic proton of optically pure diastereomers Ia and Ic, what indicates the presence of a single conformer having a bulky camphoyloxy group in quasi-equatorial position. Accordingly such a substrate should be solvolysed stereospecifically with retention of configuration. In fact, when this work was in progress, another group of authors¹¹ successfully prepared enantiomeric IIId, with retained configuration after solvolysis of enantiomeric (+)-3-hemisuccinate (Id) in ethanolic hydrochloric acid under nonaqueous conditions. In repeating the

solvolyses of Ia and Ic, both having R-configuration^{2,3} in carefully controlled anhydrous methanolic hydrogen chloride we were also able to isolate the optically active R-(+)-IIa, $[\alpha]_{578} = +23.8^{\circ}$, respectively. Optical rotation of R-(+)-IIa obtained from Ia or Ic was significantly lower than obtained for the same compound from (+)-hemisuccinate Id (lit.¹¹ $[\alpha]_{D}^{20} = +293^{\circ}$, we obtained a sample of $[\alpha]_{578} = +232^{\circ}$). This should be ascribed to much longer reaction time needed for solvolyses of Ia (4.5 h) related to solvolyses of Id (20 min) -other conditions being equal (ca. 0 °C, 10% HCl in MeOH). Summarizing the above results it can be concluded that at least two different mechanisms are at work during racemization of compounds of type II, one predominating under aqueous and the other under anhydrous conditions. Fast racemization during the solvolyses in the presence of water proceeds through formation of 3-hydroxy compounds, and their subsequent acid catalyzed racemization through a ring-chain tautomerism. This step causes racemization (Scheme 1) and is a well known process in some five membered heterocycles with two heteroatoms¹²⁻¹⁴. Furthermore, ring opening of some 3-hydroxy-1,4-benzodiazepin-2-ones at the C(3)-N(4) bond has also been achieved enzymatically¹⁵.

Slower racemization observed during methanolysis under anhydrous conditions is proposed to proceed through partially nonstereospecific identity reaction, *i. e.* multiple exchange of the alkoxy group at C(3). More detailed investigations



Scheme 1

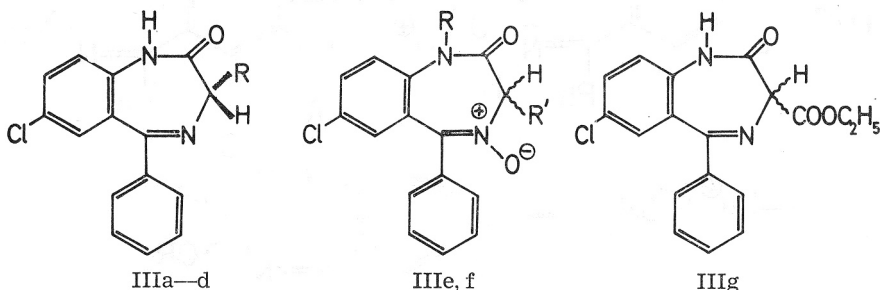
of this, and possibly others mechanistic contributions to racemization are in progress.

With these results in mind the resolution of 3-hydroxy compound IIe and 3-methoxy compound IIb has been attempted in two other ways. One of these involves preparation and resolution of their diastereomeric salts. Camphanic acid and dibenzoyl tartaric acid proved to be too weak to give stable salts with the weakly basic N(4) atom of the 1,4-benzodiazepine ring. Camphorsulphonic acid, on the other hand, gave rise to extensive decomposition of IIb, and only limited yields of one diastereomeric salt (V) possessing low optical purity, were obtained. Compound IIe decomposed with the same resolving agent, but only traces of the salt of the decomposition product 2-amino-5-chlorobenzophenone were isolated and its structure was proved by independent preparation (VIII).

After unsatisfactory resolution results *via* diastereomeric salts, chromatographic resolution of IIb on partially acetylated cellulose (Woelm) as a chiral adsorbent was attempted. Limited quantities of the optically active material were again obtained (see Experimental, Fig. 2). Samples of IIb possessing *ca.* 5% optical purity and S-configuration, as concluded from the comparison of their CD spectra with that of IIIa¹⁶, exhibited no change of rotation after heating in inert organic solvents (cyclohexane, benzene) or standing in a buffered aqueous solution. This reveals their optical stability when the possibility for the acid-catalyzed nucleophilic substitution at C(3) is excluded.

B. 3-Alkyl-1,4-benzodiazepin-2-ones

N.m.r. measurements of C(3)-H/D exchange in the compounds IIIa-e revealed no observable H/D exchange after 24 h in methanol-*d*₄ or in deuterium oxide/methanol-*d*₄ at pD = 1. This result has double importance. Firstly it offers a possibility of resolution of racemic compounds of type IIIa-c with strong chiral acids, or of purification of chemically impure enantiomers through the salts with strong mineral acids without any loss of optical purity. 3S-Enantiomers of IIIa-c have been recently prepared¹⁶ and pharmacologically tested¹ along with other derivatives of (S) or (R)- α -amino acids. Prochiral compound IIIe and chiral IIIa gave, in fact, stable camphorsulfonates VI and VII. Secondly, the stereochemistry of the Polonovski rearrangement has been recently studied¹⁸ on N⁴-oxides IIIe,f and in this connection optical stability of these compounds under acidic conditions is significant.



- IIIa-d
- | |
|---|
| R |
| a —CH ₃ (3S) |
| b —CH ₂ C ₆ H ₅ (3S) |
| c —CH(CH ₃) ₂ (3S) |
| d —H |

- IIIe, f
- | | |
|-------------------|-----------------|
| R | R' |
| e H | CH ₃ |
| f CH ₃ | CH ₃ |

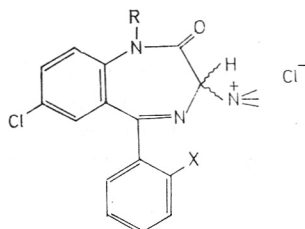
The only compound which exhibited H/D exchange and possessed exocyclic C(3)-C bond was IIIg, a derivative of α -amino-malonic acid¹⁹; their $k_{H/D}$ was found to be $3 \times 10^{-3} \text{ min}^{-1}$.

C. 3-Ammonio-1,4-benzodiazepin-2-one derivatives

Results of the H/D exchange rate measurements on compounds IVa-j performed in methanol- d_4 are listed in Table I.

TABLE I.

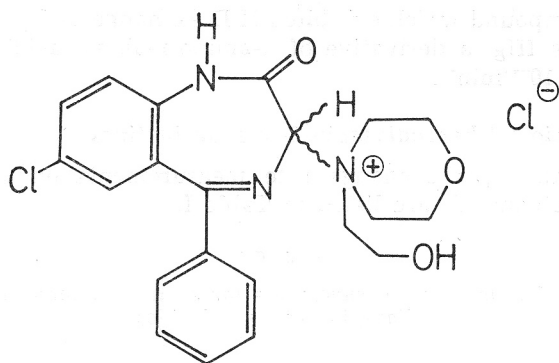
C(3)-H/D exchange rate measurements for some 3-ammonium-1,4-benzodiazepin-2-ones chlorides



Compd.	R	X	C(3)-H (ppm)	$k_{\text{obs}}/\text{min}^{-1}$	
IVa	CH ₃		6.77	3×10^{-2}	
IVb	H		6.71	5×10^{-2}	
IVc	H		Cl	—	too fast*
IVd	CH ₃		6.30	1.1×10^{-3}	
IVf	H		H	6.37	3×10^{-2}
IVg	H		Cl	6.43	3×10^{-1}
IVh	CH ₃		6.37	1.2×10^{-3}	
IVi	H		H	6.33	8.5×10^{-3}
IVj	H		Cl	6.33	2×10^{-1}

* $k_{\text{obs}} > 2$

Only compound IVk showed no disappearance of C(3)-H. signal within 18 h in sharp contrast with compounds IVa-j. Its δ for C(3)-H at 5.43 ppm revealed much higher electron density about this proton than in IVa-j (see Table I). Two main structural features in IVa-j seem to be responsible for different H/D exchange rates within derivative groups with the same



tertiary amine. The *N*-methyl group causes rate retardation, and the *ortho*-chlorine atom in the 5-phenyl group enters hydrogen bonds with C(3)-H (Fig. 1), thus leading to a rate enhancement of H/D exchange. The latter phenomenon is suggested by an examination of space filling CPK-models.

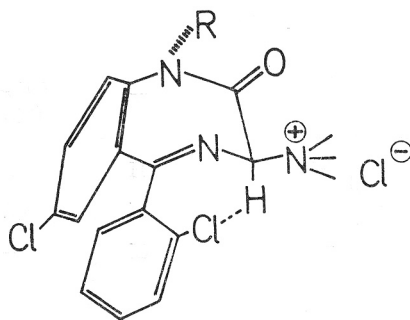


Fig. 1

Compounds of the type IV have been recently prepared as a new water-soluble derivatives of 1,4-benzodiazepin-2-ones, and exhibited highly interesting pharmacological properties²⁰. In this connection the above results of H/D exchange rate measurements allow some general conclusions. Chiral quaternary derivatives of 1,4-benzodiazepin-2-ones with any pyridine-like optically active amine (Type IVa-j) are of no pharmacological importance, even when prepared and resolved under carefully controlled conditions, because of a fast H/D exchange and consequent racemization. A quite opposite behaviour, *i. e.* high optical stability, is to be expected from the quaternary salts of a strongly basic tertiary aliphatic amines which are devoid of conjugative stabilization of a carbanion at C(3), as in the case of quaternary salts of some alkaloids.

EXPERIMENTAL

Melting points were determined on a Kofler microheating stage and are uncorrected. I. r. spectra were recorded on a Perkin-Elmer M-137 Spectrophotometer in KBr pellets. Optical rotations were measured on a Perkin Elmer M-141 polarimeter at room temperature. CD-spectra were measured at Lehrstuhl für Chemie, Ruhruniversität in Bochum, by courtesy of Prof. G. Snatzke.

Kinetic measurements

Racemization rate measurements were performed on NPL automatic polarimeter 143D at $[\alpha]_D$ and $(25 \pm 0.1)^\circ\text{C}$, using VEB Type U6 thermostat and double-walled cell.

N.m.r. spectra were obtained, and kinetical measurements were performed on a Varian T-60 spectrometer at $(35 \pm 0.1)^\circ\text{C}$. All deuterated solvents used were purchased from Stohler Isotope Chemicals. About 0.1 mmol of each substance was weighed with ± 0.1 mg accuracy and dissolved in 0.50 ml of methanol- d_4 . The results were represented as exemplified by Table II.

TABLE II.

Compound IVh (34.7 mg, 0.083 mmol) dissolved in CD_3CD (0.50 ml). Starting concentration of protons was calculated to 3.0 mol/mol XIV. Included are all exchangeable—NH, and OH protons from the substrate as well as protons from the hydroxyl group of the solvent.

No.	<i>t</i> /min	<i>I</i> /mm	% C(3)-H	<i>St</i> /mm
1	0	—	100	—
2	40	6.5	93	21/3
3	98	6	86	21/3
4	158	6	86	21/3
5	232	6	71	21/3
6	341	4.5	64	21/3
7	510	4.5	61	22/3
8	820	2.5	34	22/3
9	1440	1.5	20	22/3

No. Sequence number of measurement

t Period of time between dissolution of the substance and C(3)-H integral measurement.

I Signal intensity observed for C(3)-proton

% *H* Percent intensity calculated from the theoretical intensity for C(3)-H as obtained from

St Standard signal intensity which resulted from the total integral of the integral standard $\text{N}^1\text{-CH}_3$, or some other group when this one is absent.

H/D exchange rates were determined in triplicate and average values were taken for calculations of k_{obs} . The pseudo-first order rate constants have been evaluated from the kinetic data by means of a non-linear least-squares program on a computer and are listed in Table I. The computer program is based on the Los Alamos Sci Lab. Reports LA 2367 and Addenda.

7-Chloro-1-methyl-1,3-dihydro-3-methoxy-5-phenyl-2H-1,4-benzodiazepin-2-one, (+)-Camphorsulphonate (V)

Compound IIB, (314 mg, 1 mmol) and (+)-camphorsulphonic acid (234.4 mg, 1 mmol) were dissolved in hot benzene (20 ml) and then set aside for crystallization at room temperature. After three days crystals were collected: 161 mg, m.p. 150–155°C. Two recrystallizations gave the pure salt, m.p. 162–166°C (dec.). I.r. (KBr) 2460–3350 (broad), 1740, 1722, 1620, 1596, 1475, 1280, 1260, 1040, 930, 781, 750, 703, 690 cm^{-1} . $[\alpha]_{578} + 17.7^\circ$, $[\alpha]_{546} + 21.4^\circ$ ($c = 2.038$, CHCl_3). CD (ethanol) + 2.46 (289 nm); (S)-enantiomer enriched, no estimation of the optical yield is, however possible.

Anal. $\text{C}_{27}\text{H}_{31}\text{ClN}_2\text{O}_6\text{S}$ (546.07) Calcd.: C 59.40; H 5.72; N 5.13%
Found: C 59.24; H 5.90; N 3.32%

7-Chloro-1-methyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one
(+)-camphorsulphonate (VI)

(+)-Camphorsulphonic acid (230 mg) was dissolved in hot benzene (20 ml) and a solution of 7-chloro-1-methyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (280 mg, 1 mmol) in benzene (3 ml) was added. After crystallization on ice for 24 h, crystals were collected, washed with benzene, and dried (429 mg, 85%, m. p. 200—208 °C (dec.), i. r. (KBr) 2350—3000 (broad), 1742, 1695, 1647, 1480, 1349, 1275, 1260, 1235, 1157, 1146, 1040, 780, 741 and 705 cm^{-1} ; $[\alpha]_{578} + 29.7^\circ$, $[\alpha]_{546} + 34.5^\circ$ ($c = 2.29$ in CHCl_3).

Anal. $\text{C}_{26}\text{H}_{29}\text{ClN}_2\text{O}_5\text{S}$ (516.05) Calcd.: C 60.52; H 5.56; N 6.43%
Found: C 60.78; H 5.58; N 6.13%

7-Chloro-1,3(S)-dimethyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one
(+)-camphorsulphonate (VII)

Compound IIIa (852 mg, 3.0 mmol) was dissolved in hot ether (40 ml) and a solution of (+)-camphorsulphonic acid (696 mg, 3.0 mmol) in acetone (8.0 ml) added. The yellow oil crystallized on stirring. After chilling the crystals were separated and dried, yield 1.51 g (94.5%), m. p. 155—159 °C; $[\alpha]_{578} - 156.5^\circ$ ($c = 1.00$ in MeOH).

Anal. $\text{C}_{26}\text{H}_{29}\text{ClNO}_5\text{S} \times \text{H}_2\text{O}$ (535.06) Calcd.: C 58.37; H 5.84; N 5.24%
Found: C 58.38; H 6.12; N 5.02%

2-Amino-5-chloro-benzophenone (+)-camphorsulphonate (VIII)

2-Amino-5-chloro-benzophenone (232.4, 1.0 mmol) and (+)-camphor sulphonic acid (234, 1.0 mmol) were dissolved in hot benzene (20 ml) and crystallized at room temperature overnight. Crystallization afforded 250 mg of V, m. p. between 70—80 °C. After repeated recrystallization from benzene rose the m. p. to 92 °C (dec.).

Anal. $\text{C}_{23}\text{H}_{26}\text{ClNO}_5\text{S}$ (463.98) Calcd.: C 59.4; H 5.65; N 3.02%
Found: C 59.24; H 5.90 N 3.32%

Ethanolysis of diastereomeric esters Ia and Ic

Ia. — Compound Ia (the faster moving diastereomer on silica², possessing 3R-configuration, 400 mg) was dissolved in ca. 5% dry ethanolic hydrogen chloride (10 ml). After 4.5 h standing at room temperature, the solution was neutralized with 10% aqueous NaAc, evaporated and the residue washed with water (20 ml) and extracted with chloroform (3 × 15 ml). The organic phase was dried (Na_2SO_4), evaporated and dried at 0.1 mmHg (P_2O_5). Spec. rotation obtained IID $[\alpha]_{578} + 46.6^\circ$ ($c = 1.02$ in dioxane).

Ic. — Compound Ic (the faster moving diastereomer on silica³, possessing 3R-configuration, 150 mg) was dissolved in ca. 5% dry ethanolic hydrogen chloride (5 ml) and treated in the same way as described for Ia. Spec. rotation of IIC obtained was $[\alpha]_{578} + 23.8^\circ$ ($c = 0.76$ in DMSO).

Chromatographic Separation of Racemic 7-Chloro-1-methyl-3-methoxy-1,3-dihydro-2H-5-phenyl-1,4-benzodiazepine-2-one (IIb)

In order to obtain qualitative control of column chromatography, t.l.c. plates (2.5 × 7) were prepared as follows: Microcrystalline cellulose (Whatman, 10g) was slurried in water (35 ml) and ZnS (0.2 g) as fluorescent indicator was added. After 5 min grinding in a mortar, glass-plates were coated and dried overnight at room temperature. Spots were made visible under a u. v. (254 nm) lamp. Using this technique cyclohexane proved to be the most promising solvent for chromatographic separation of the enantiomers of IIb. In this solvent, as in a number of others tested, no separation of the two spots for the enantiomers could be obtained, but one diffuse spot with $R_f = 0.05-0.3$ indicated that partial enrichment of the

enantiomers is to be expected in the first and last fractions from the column. Column chromatography was performed using acetylated cellulose (2.5 mol Acyl/mol cellulose, Woelm), which was slurried in cyclohexane before the application to a column (150 × 0.8 cm).

The column II_f (500 mg) was adsorbed on 2 g of cellulose after dissolution in ether (50 ml) and after evaporation was applied on to the column. Fractions (5 ml pro fraction) were checked by t.l.c. and rotation measurements. Results of a typical experiment are given in Fig. 2.

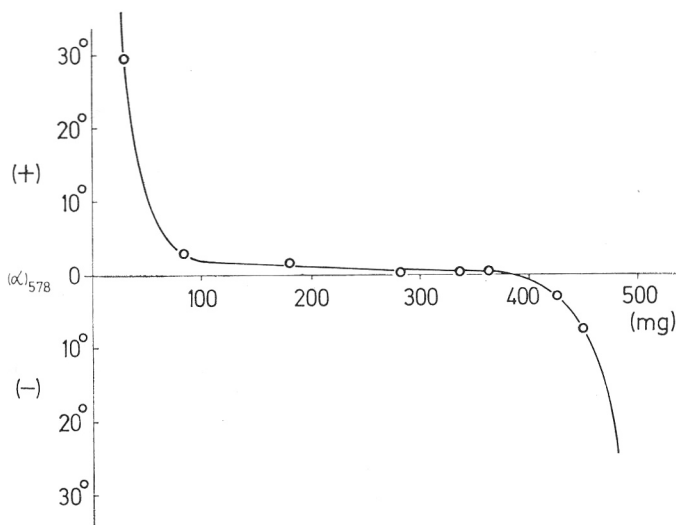


Fig. 2. Resolution of (±)-II_f by column chromatography on acetylcellulose (Woelm) as a chiral adsorbent.

Fractions 34–35 (23.7 mg, $[\alpha]_{578} + 30.6^\circ$ (in CHCl_3); and 114–145 (34.9 mg $[\alpha]_{578} - 7.2^\circ$ (in CHCl_3) gave identical n.m.r. spectra (CDCl_3); 3.42 ppm (s, 3H), 3.63 (s, 3H), 4.66 (s, 1H), 7.2–7.8 (m, 8H). A sample possessing $[\alpha]_{578} + 16.6^\circ$ (in CHCl_3) exhibited the following CD (ethanol); 19 (317 nm), +0.77 (286 nm), and +1.19 (261 nm). The Cotton effect reveals (S) configuration of this enantiomer as compared with CD of (S)-IIIa (in acetonitrile); -7.75 nm), +8.62 (285 nm), and 37.32 (259 nm), while values indicated an optical purity of ca. 4–5%.

Other four experiments of chromatographic separations performed with some minor modifications of the above procedure gave a fraction which possessed $[\alpha]_{578} + 35.9^\circ$ (in CHCl_3) i.e. ca. 10% optical purity.

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SAŽETAK

Kiralni 1,4-benzodiazepini. VIII. O brzini izmjene i optičkoj stabilnosti kiralnog centra C(3)

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Različiti kiralno supstituirani 1,4-benzodiazepini-2-oni s 3-hidroksi- i 3-alkoksi- (opća formula I), 3-aciloksi- (opća formula II), 3-alkil- (opća formula III) i 3-kvartnom amonijevom skupinom (opća formula IV) kao supstituentom, podvrgnuti su mjerenju brzine izmjene C(3)-H/D u namjeri da se dobije uvid u optičku stabilnost kiralnog centra i mehanizam racemizacije. Samo spojevi tipa IVa—j pokazali su izmjenu H/D, iako su uz kiselu katalizu racemizirali i spojevi tipa I i II, upućujući na neki drugi mehanizam u tom procesu. Spojevi tipa III, bilo kao slobodne baze (IIIa—c), N⁴-protonirane kiseline, ili N⁴-oksidi (IIIe, f), nisu podlijegali izmjeni H/D, a također su i optički stabilni. U slučajevima gdje se može isključiti mehanizam deprotoniranja—reprotoniranja, diskutiraju se dva druga mehanizma racemizacije, tj. kiselinom katalizirana tautomerija prsten—lanac i identitetna supstituciona reakcija alkoksidnim ionima.

CRC, COMPAGNIA DI RICERCA CHIMICA, CHIASSO, ŠVICARSKA

INSTITUT ZA ORGANSKU KEMIJU I BIOKEMIJU, SVEUČILIŠTE Primljeno 17. lipnja 1974.
U ZAGREBU, 41000 ZAGREB

i

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