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RESTRICTED CONFORMATIONAL PROCESSES IN 10,11-DIHYDRO-5H-DIBENZ[b,f]AZEPINE DERIVATIVES. A DNMR STUDY.

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Abstract. A variable temperature 300 MHz NMR investigation of *trans*-10-bromo-10,11-dihydro-11-hydroxy-5H-dibenz[b,f]azepine-5-carbonyl chloride has shown the presence of two conformationally restricted isomers, both bearing anti oriented α protons and hydrogen bonded gauche substituents at C(10) and C(11), which are interconverted through ring inversion by torsion about the C(4a)-N(5)-C(5a) bonds. The free energy of activation for the ring inversion process, obtained in the 21-38 °C temperature range, is $\Delta G^{\ddagger}$ = 16.5±0.2 Kcal mol^{-1}.

The 10,11-dihydro-5H-dibenz[b,f]azepine ring system is of considerable pharmacological interest, being present both in antidepressant drugs and in metabolites of several drugs having the 5H-dibenz[b,f]azepine parent structure.[1] A deeper knowledge of the conformational behaviour of this tricyclic system could be of help in understanding the basis of the biological activity of these compounds.

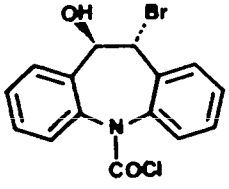
In the course of previous investigations we observed that the ^{1}H NMR spectra of the 5-carbonyl chloride and 5-carboxyamide derivatives of 10,11-dihydro-5H-dibenz[b,f]azepine having two trans hydroxyl groups or bromine atoms at the 10 and 11 positions exhibit a nonequivalence of the H(10) and H(11) protons,[2,3] pointing to the occurrence of restricted conformational processes in the seven-membered azepine ring. In this paper we are reporting on the NMR observation at room temperature of two nonequivalent gauche conformers when two different trans substituents are present at C(10) and C(11).

The 80 MHz ^{1}H NMR spectrum of *trans*-10-bromo-10,11-dihydro-11-hydroxy-5H-dibenz[b,f]azepine-5-carbonyl chloride (1) in chloroform-*d* showed for the H(10) and H(11) protons an AB pattern at δ 5.7 and 5.25 ppm with a coupling constant of about 9 Hz, with a considerable broadening of the lower field doublet persisting also after exchange with D_2O. A splitting of this doublet into four lines was clearly apparent in methanol-d_4. In acetonitrile-d_3 further splittings were observed for this signal, as well as for the OH signal, which were removed after exchange with D_2O, showing that the couple of doublets at lower field corresponded to protons α to hydroxyl. Two sharp lines were instead always observed for the higher field doublet. Furthermore, one of the aromatic protons

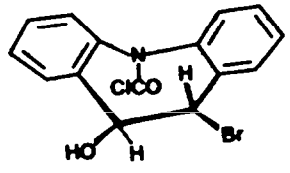
resulted to be more deshielded with respect to the remaining ones, appearing as a multiplet integrating for 1 H, well separated from a complex absorption due to seven overlapping aromatic protons.

At 300 MHz, two partially overlapping doublets of different intensity and slightly different coupling constant, J = 9.6 and 8.7 Hz, were observed also in chloroform-*d* at δ 5.72 and 5.68 ppm, and a doublet with a splitting of 9 Hz still appeared at δ 5.28 ppm. The two lower field doublets were well separated (δ 5.71 and 5.62 ppm, J 9.4 and 8.1 Hz), in the 300 MHz spectrum in methanol-d_4. In this solvent a splitting of the higher field line and some broadening of the lower field one was also observed for the other signal at δ 5.35 ppm, thus showing that the entire medium field part of the spectrum of 1 actually consisted of two AB systems. A very similar spectrum was observed also in acetonitrile-d_3. In all three solvents the more deshielded aromatic proton appeared as a couple of partially overlapping doublets of different intensity, with similar J_{ortho} of about 7.5 Hz and a small meta coupling producing some broadening of each line.

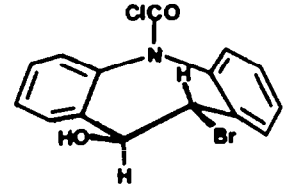
The IR spectrum of bromohydrin 1 in dilute solution ($5 \cdot 10^{-4}$ M) of carbon tetrachloride showed a hydroxyl stretching band at 3580 cm^{-1} and no absorption above 3600 cm^{-1}, where the free O-H stretching absorption is usually found,[4] indicating the presence of an intramolecular hydrogen bond between hydroxyl and the adjacent bromine. The occurrence of a relatively strong hydrogen bond was also suggested by an unusually slow rate of exchange with D_2O observed in the chloroform-*d* NMR spectrum.



1



1a



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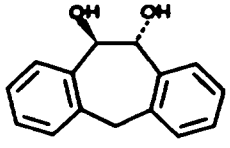

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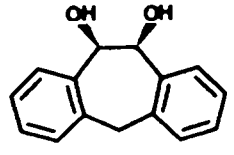

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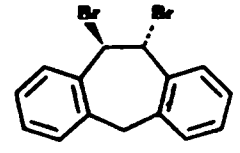

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The data indicated the presence in solution of two conformers of the bromohydrin, **1a** and **1b**, both bearing anti oriented α protons and gauche substituents at C(10) and C(11). These two conformers have unequivalent protons α to OH, accidentally equivalent or slightly unequivalent protons α to Br, and unequivalent protons in only one position of the two aromatic rings. This position was expected to be one of the four (C(1), C(4), C(6), C(9)) adjacent to the seven-membered ring, where the hydroxyl, the carbonyl chloride and the bromine atom are respectively located.

An extra deshielding of the two aromatic protons at C(1) and C(9), adjacent to the hydroxyl groups, was observed in the 300 MHz chloroform-*d* spectra of both *trans*-(**2**) and *cis*-10,11-dihydro-10,11-dihydroxy-5H-dibenzo[a,d]cycloheptene (**3**), where a methylene bridge is present in place of the NCOCl group. Isolated doublets with J = 7.5 Hz, integrating for 2 H, were found at δ 7.61 and δ 7.56 ppm, for the trans and cis isomer respectively, downfield from the overlapping absorption of the other aromatic protons at δ 7.2-7.4 ppm. No such extra deshielding of the C(1) and C(9) protons was instead observed for *trans*-10,11-dibromo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (**4**). These observations point to C(1) as the site of the observed nonequivalence of aromatic protons in the two conformers of bromohydrin **1**.

The NMR assignment and the relative coupling constants in the three solvents are summarized in Table I.

Table I. NMR parameters of the two conformers **1a** and **1b** of *trans*-10-bromo-10,11-dihydro-11-hydroxy-5H-dibenz[b,f]azepine-5-carbonyl chloride at 21 °C.

Solvent	$\delta_{1,1}$	$J_{1,2}$	$\delta_{2,2}$-$_{9,9}$	$\delta_{10,10}$	$\delta_{11,11}$	$J_{10,11}$	Conformer ratio
$CDCl_3$	7.78 7.74	7.5	7.29-7.49	5.28	5.72 5.68	9.6 8.7	40:60
CD_3OD	7.83 7.79	7.5	7.39-7.61	5.35	5.71 5.62	9.4 8.1	41:59
CD_3CN	7.71 7.67	7.5	7.32-7.60	5.31	5.61 5.52	9.3 8.1	43:57

Variable temperature 300 MHz NMR spectra were taken in chloroform-*d* and methanol-d_4 in the 21-51 °C range. In the first solvent with increasing temperature the couples of doublets due to the protons at C(11) and C(1) tended to coalesce with identical dynamics. The same occurred in methanol-d_4 where, furthermore, the splitting of the higher field line of the δ 5.35 signal disappeared giving a sharp doublet.

Figure 1 shows the relevant part of the 300 MHz spectra of **1** in chloroform-d at 21 °C and at 51 °C.

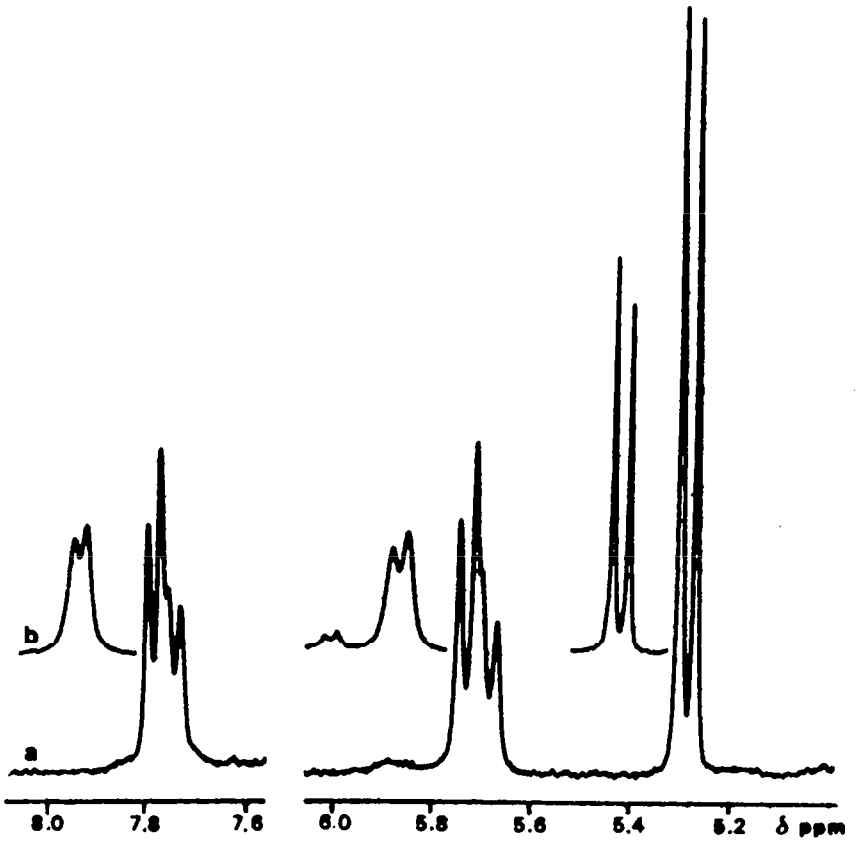

Figure 1. Signals of the protons at C(1), C(10) and C(11) in the 300 MHz NMR spectrum of 10-bromo-11-hydroxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carbonyl chloride in chloroform-*d* at 21 °C (a) and 51 °C (b).

The dynamic process was analyzed using the band shapes of the signals relative to the protons at C(10) and C(11) in $CDCl_3$. The chemical shifts of the sensor nuclei, reported in Table I, were assumed to be independent of temperature. A natural line width of 1.55 Hz was evaluated from the spectrum at 21 °C. On the basis of the conformer population ratio, also deduced from the spectrum at 21 °C (see Table I), a free energy difference of 0.25 Kcal mol^{-1} between the two conformations was computed. The population ratios at the other temperatures of interest were consequently determined. A single rate process was assumed and theoretical band shapes were computed with the DNMR 3 program,[8] using the chemical shifts, the population ratios and the line width determined as mentioned and with trial kinetic constants k. By visually comparing the simulated spectra with the experimental ones, an appropriate set of $k(T)$ values, ranging from 4.29 to 11.3 sec^{-1}, was found for the seven spectra recorded between 21 and 38 °C. Two exemples of experimental and computed band shapes are shown in Fig 2. At temperatures higher than 38 °C a good simulation required a substantial and progressive increase of the natural line width. Moreover, the spectral baseline showed the rising of small new bands at δ = 5.85 (see Figure 1). These fact might perhaps be ascribed to the activation of a second dynamic process. The information contained in the higher temperature spectra, however, was inadequate for a significant analysis of this process and only the data relative to the 21-38 °C temperature interval were considered further.

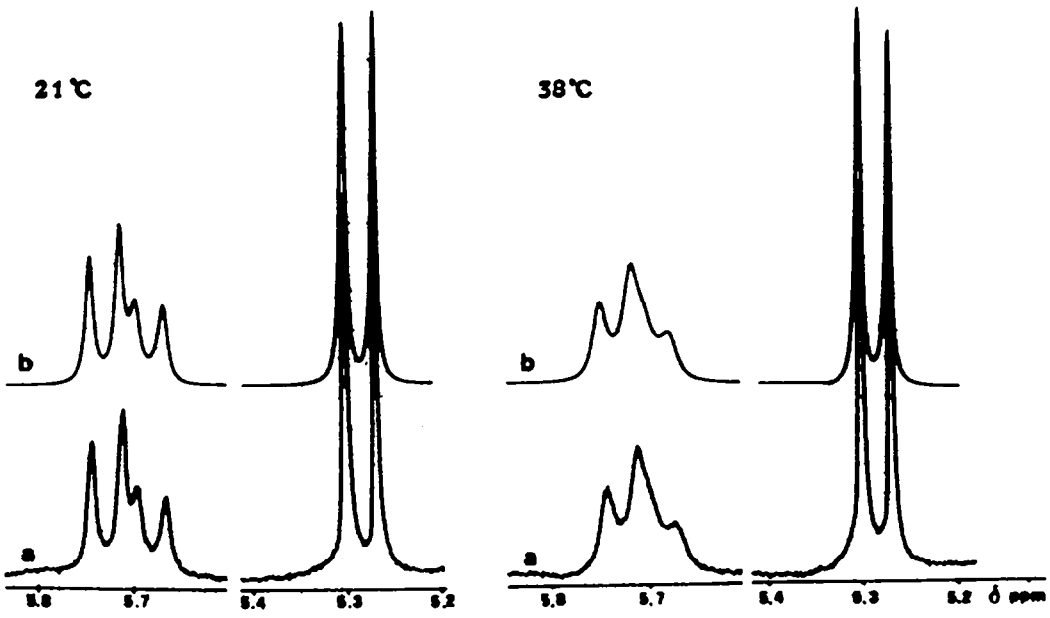

Figure 2. Experimental (a) and computed (bH) band shapes of the signals of protons at C(10) and C(11) in the 300 MHz NMR spectrum of 10-bromo-11-hydroxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carbonyl chloride in chloroform-d at 21 °C and 38 °C.

The Eyring equation, $k = (K_B T/h)e^{-\Delta G^{\ddagger}/RT}$, was used in its logarithmic form in order to determine $\Delta G^{\ddagger}$ from the experimental $k(T)$ values for the conformational process under investigation. The calculation was performed by means of a least squares fitting program and terminated with a RMS error of 0.07. The result for the free activation energy is $\Delta G^{\ddagger}$ = 16.5±0.2 Kcal mol^{-1}. The quoted uncertainity largely overwhelms the standard deviation produced by the fitting procedure; it is evaluated by taking into account possible errors on the temperature values of up to ± 3 °C and on the population ratios of up to 10%.[6]

It has been recognized[7-9] that three independent restricted conformational processes can coexist in 10,11-dihydro-5H-dibenz[b,f]azepine derivatives: 1) rotation around the N-CO bond; 2) twisting of the C(10)-C(11) bond; 3) ring inversion by torsion about the C(4a)-N(5)-C(5a) bond. It was also pointed out[7-9] that in N-acyl substituted derivatives process 3) should be precluded unless process 1) is simultaneously operating, since the plane of the carbonyl group should be perpendicular to the C(4a)-N(5)-C(5a) plane in order to minimize its repulsions with the aromatic hydrogens at C(4) and C(6) during ring inversion. The temperature dependent NMR spectra of the 5-acetyl, 5-chloroacetyl, and 5-ethoxycarbonyl derivatives of the parent 10,11-dihydro-5H-dibenz[b,f]azepine structure have been interpreted on the basis of a concerted rotational-inversion process of this type.[7,8] Evidence for restricted processes of type 2) and 3) but not for amide rotational isomers due to a restricted process 1) was obtained in a 100 MHz ^1H NMR investigation of 5-acetyl-10-cyano-10,11-dihydro-5H-dibenz[b,f]azepine.[9]

The present results are consistent with a restricted twisting of the C(10)-C(11) bond and a simultaneously restricted ring inversion by torsion about the C(4a)-N(5)-C(5a) bonds as the origin of the freezing of bromohydrin 1 in the two

conformers **1a** and **1b** at room temperature. In fact, the observed large values of $J_{10,11}$ are typical of anti oriented protons α to electronegative substituents. Process 2), which is normally the least energy demanding of the three above discussed conformational processes, appears thus to be hampered by the presence of the hydroxyl and bromine substituents which, at least in non hydroxylic solvents, are held in a gauche orientation by hydrogen bonding.

The clear spectral changes found in the 21-38 °C temperature range are instead certainly due to the activation of a conformational interchange between **1a** and **1b** by torsion about the C(4a)-N(5)-C(5a) bonds. The small but significant difference in the population of these two conformers, similar in all investigated solvents, could be expected on the basis of the different orientation of the 10 and 11 substituents relative to the planes of the aromatic rings: in **1a** both the hydroxyl and the hydrogen at C(11) lie on the same side and the bromine and hydrogen at C(10) lie on opposite sides with respect to the adjacent phenyl ring, while the contrary is true for conformer **1b**

The free energy of activation for this ring inversion process found in the present investigation, $\Delta G^{\ddagger} = 16.5 \pm 0.2$ Kcal mol^{-1}, is comparable with those obtained, using approximate treatments, for the above mentioned rotational-inversion process in 5-acyl-10,11-dihydro-5H-dibenz[b,f]azepines.[8] Restricted rotation around the N-CO bond would be anticipated also for bromohydrin **1**, since X-ray diffraction of the corresponding 10,11-*trans*-dibromide has shown bond angles at N(5) near to 120° and a quite short N-CO bond.[2] No conclusive evidence for the presence at room temperature of restricted conformational isomers of this type was obtained, however, in the present investigation. Non equivalent aromatic protons were, in fact, found only at C(1), and not at the carbons ortho to nitrogen, C(4) and C(6), as could be expected for different rotamers around the N-CO bond. The failure to observe distinct rotamers does not necessarily involve free rotation, however, since either the spectral differences between restricted rotamers may be too small to be detected or only one rotamer may be substantially populated. Further investigations are being planned in order to obtain more complete information about the conformational processes operating in the presently examined and in related tricyclic systems of pharmacological interest.

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian CFT 20 and a Varian XR 300 instruments. IR spectra were determined with a Perkin Elmer 1750 FT spectrophotometer.

***trans*-10-Bromo-10,11-dihydro-11-hydroxy-5H-dibenz[b,f]azepine-5-carbonyl chloride (1)**: This compound, mp 148-150 °C, was prepared by ring opening of 1a,10b-dihydro-6H-dibenz[b,f]oxireno[d]azepine-6-carbonyl chloride with HBr, as reported.[3]

***trans*-10,11-Dihydro-10,11-dihydroxy-5H-dibenzo[a,d]cycloheptene (2)**: 5H-dibenzo[a,d]cycloheptene[10] (1.2 g, 6 mmol) was added to a solution of silver benzoate (2.7 g, 11.7 mmol) and I_2 (1.6 g, 6 mmol) in anhydrous benzene (50 ml) and the mixture was refluxed for 8 h. After cooling, the precipitate was filtered off and the solution was washed with 10% aqueous Na_2CO_3 and water, dried ($MgSO_4$) and evaporated in vacuo. The crude residue (0.9 g) was dissolved in a solution of KOH (0.9 g) in EtOH (17 ml) and refluxed for 1 h. The solution was then neutralized and extracted with AcOEt and the extract was dried ($MgSO_4$)

and evaporated in vacuo. The residue was crystallized from $CHCl_3$, to give 0.45 g (2 mmol) of pure **2**, mp 180-181 °C. ^1H NMR ($CDCl_3$): δ 2.0 (2H, OH); 4.08 (s, 2H, CH_2); 5.06 (s, 2H, CHOH); 7.15-7.40 (m, 6H, aromatic protons at C(2)-C(8)); 7.61 (d, 2H, aromatic protons at C(1) and C(9), J 7.5 Hz).
Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.23
Found: C, 79.94; H, 6.16.

***cis*-10,11-Dihydro-10,11-dihydroxy-5H-dibenzo[a,d]cycloheptene (3):** 5H-dibenzo[a,d]cycloheptene (0.2 g, 1 mmol) and OsO_4 (0.26 g, 1 mmol) were reacted in benzene (30 ml) and pyridine (0.5 ml) at room temperature for 4 days. The precipitate was then collected, added to an aqueous solution (5 ml) of mannitol (0.26 g) and KOH (0.7 g), and the mixture was stirred at room temperature for 24 h. The formed precipitate, consisting of crude **3**, was collected and crystallized from EtOH to give pure **3** (0.12 g), mp 176-178 °C. ^1H NMR ($CDCl_3$): δ 1.85 (2H, OH); 3.37 (d, 1H, CH_2, J 15 Hz); 4.36 (d, 1H, CH_2, J 15 Hz); 5.29 (s, 2H, CHOH); 7.15-7.46 (m, 6H, aromatic protons at C(2)-C(8)); 7.56 (d, 2H, aromatic protons at C(1) and C(9), J 7.5 Hz).
Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.23.
Found: C, 79.52; H, 6.23.

***trans*-10,11-Dibromo-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (4).** A 10^{-1} M 1,2-dichloroethane solution of Br_2 (25 ml) was added to 5H-dibenzo[a,d]cycloheptene (0.38 g, 2 mmol) in 5 ml of the same solvent. After stirring for 3 h at room temperature, the solution was washed with saturated $NaHSO_3$ and water, dried ($MgSO_4$) and evaporated in vacuo to give 0.6 g of crude dibromide, that was crystallized from acetonitrile to give pure **4**, mp between 150 and 160 °C (depending on the rate of heating) with gas evolution (lit.[1] mp between 155 and 163 °C with evolution of a gas). ^1H NMR ($CDCl_3$): δ 4.54 (s, 2H, CH_2); 5.85 (s, 2H, CHBr); 7.20-7.38 (m, 8H, aromatic protons).
Anal. Calcd for $C_{15}H_{12}Br_2$: C, 51.17; H, 3.43.
Found: C, 50.8; H, 3.25.

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References and notes

1. L.J. Kricka and A. Ledwith, *Chem.Rev.*, 1974, **74**, 101.
2. G. Bellucci, G. Berti, C. Chiappe, A. Lippi and F. Marioni, *J. Med. Chem.*, 1987, **30**, 768.
3. G. Bellucci, R. Bianchini, C. Chiappe, F. Marioni and R. Spagna, *J. Amer. Chem. Soc.*, 1988, **110**, 546.
4. M. Tichy' in "Advances in Organic Chemistry"; Interscience, New York, 1965; Vol. 5, p. 115.
5. D.S. Stephenson and G. Binsch, *Quantum Chem. Progr. Exch.*, 1978, **10**, 365.

6. An uncertainty of 0.2 Kcal mol^{-1} on $\Delta G^{\ddagger}$ is cited as typical of this kind of determination. See: G. Binsch and H. Kessler, *Angew. Chem. Int. Ed.*, 1980, **19**, 411.
7. R.J. Abraham, L.J. Kricka and A. Ledwith, *J. Chem. Soc. Chem. Comm.*, **1973**, 282.
8. R.J. Abraham, L.J. Kricka and A. Ledwith, *J. Chem. Soc. Perkin II*, **1974**, 1648.
9. C.R. Ellefson, L.Swenton, R.H. Bible and P.M. Green, *Tetrahedron*, 1976, **32**, 1081.
10. R.R. Fraser and R.N. Renaud, *Canad. J. Chem.*, 1970, **48**, 746.
11. S.J. Cristol and R.K. Bly, *J. Amer. Chem. Soc.*, 1960, **82**, 6155.