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Circular Dichroism of Optically Active 1,4-Benzodiazepines*

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Assignment of the CD-bands of 1,4-benzodiazepin-2-one derivatives (**1—14, 26**), and their 2-deoxo-congeners (**15—25**) has been performed by applying the qualitative MO theory and the exciton coupling theory. It has been found that the longest wavelength band (about 310 nm), as well as that around 250 nm correspond to the B_{2u} and B_{1u} transition of the chiral partial chromophore A, respectively, while the corresponding transitions for the partial chromophore C give rise to the bands at 285 nm and 250 nm (Figures 2—4). The CD-signs for several of these Cotton effects can be derived in a nonempirical manner. 7-Nitro derivatives, **23—25** scape above analysis, however, since the nitro-group is a very strong perturber, which has its own absorption bands in the same region. Model cyclic and acyclic compounds **27—36** have been prepared, and their CD-spectra analysed in the same way.

INTRODUCTION

The CD of a few optically active 1,4-benzodiazepines has been published[1-3], although only few tentative band assignments have been tried. LD spectra of some 1,4-benzodiazepines and corresponding nitrones have been recently reported[4] and reveal more transitions than the UV spectra, but still less than

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** Dedicated to Prof. E. Ziegler, Graz, on the occasion of his 70th birthday.

the CD spectra. A number of such compounds with (3**S**)- and (3*R*)-configuration have been synthesized by our group for biochemical investigations[5,6], and in the following we report on their UV- and CD-data and their interpretation.

RESULTS AND DISCUSSION

A. 1,4-Benzodiazepin-2-ones

1,4-Benzodiazepin-2-ones show up to 8 bands in their CD-spectra. These at the shortest wavelengths (VIII, below 195 nm) could not always be fully recorded and were sometimes even completely lost in the noise level. As an example the CD-spectrum of **2** (**3S**-configuration) is given in Figure 1. Band

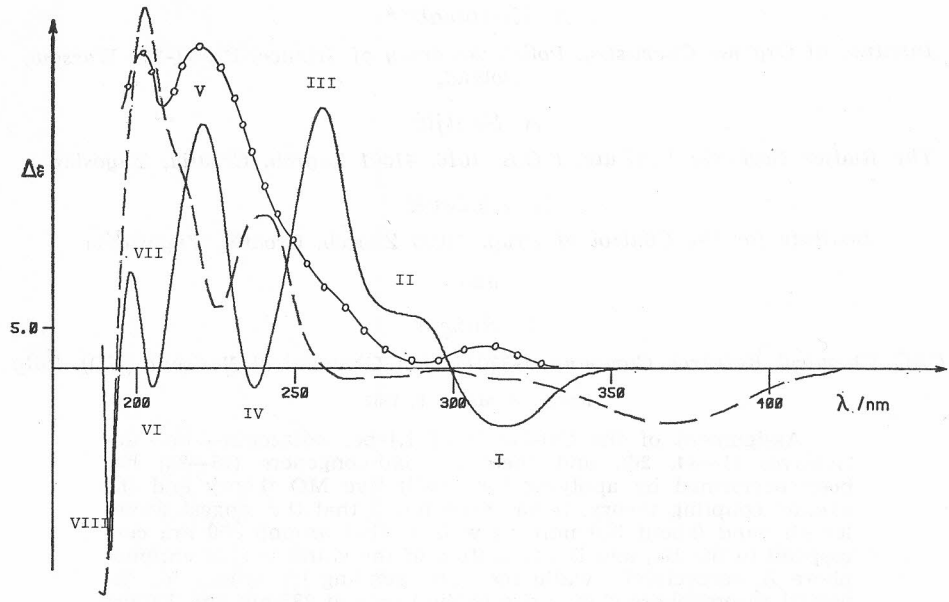
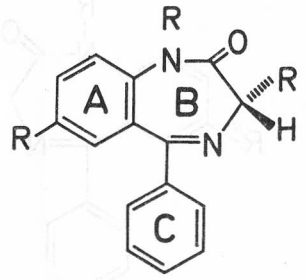


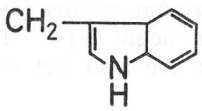
Figure 1: CD-spectrum of 2 in acetonitrile solution (———) and in acetonitrile + TFA (- - - - -), as well as UV-spectrum of 2 (—○—○—○—).

I at 316 nm (acetonitrile solution) is strongly negative, the second one (II, around 285 nm) forms only a (positive) shoulder on the long-wavelength side of the third (III) around 260 nm, which is the most intense one. The fourth (IV, 237 nm) and the sixth one (VI, around 210 nm), both slightly negative, could easily be mistaken for minima between the nearest maxima. CD-bands V (around 221 nm, very intense) and VII (198 nm, strong) are both positive, while CD-band VIII has opposite sign. In the UV-spectrum of **2** band I is also distinctly recognizable ($\varepsilon = 2000$)*, and the main maximum appears at 224 nm ($\varepsilon = 34\,400$), so it corresponds to CD-band V. Two shoulders show up on this band, one around 253 nm ($\varepsilon \approx 14\,000$) and the other at about 241

* Note: ε Values are expressed in 10^3 cm^2 mol^{-1}

nm ($\varepsilon \approx 21\,000$). The chromophoric system, due to the presence of the seven-membered ring, is not coplanar but strongly chiral, as was proved by X-ray analysis[7–12] of several 1,4-benzodiazepin-2-one derivatives and by NMR-



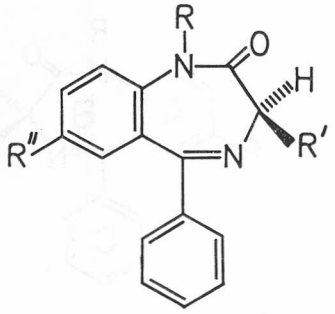
	R	R'	R''
1	H	CH_3	H
2	H	CH_3	Cl
3	H	i-Pr	Cl
4	H	$CH(OH)CH_3$	Cl
5	H	$CH_2C_6H_5$	Cl
6	H	$CH_2C_6H_4OH(p)$	Cl
7	H		Cl
8	CH_3	CH_3	Cl
9	CH_3	$CH_2C_6H_5$	Cl
10	(S)-$CHCH_3C_6H_5$	H	Cl
11	(S)-$CHCH_3C_6H_5$	OH	Cl

studies[13–14]. The barrier for the ring inversion from one conformation into its enantiomeric one was found to be of the height of appr. 50—75 kJ/mol (12—18 kcal/mol)[13,15].

The seven-membered ring adopts boat conformation and the substituent connected to the center of chirality (C-3) has to be preferentially in the quasiequatorial position, thus rings A and B form a very rigid moiety. As discussed in more detail in a recent paper[3b] the chiral ring conformation

can be described as **P** or **M***. For the (**3S**)-configuration (**1** through **9**, **11**) the **M**-conformation is the energetically stable one.[7–14]

The phenyl ring at C-5 could possess a certain degree of freedom, however the balance between resonance stabilization (coplanarity of phenyl ring with



	R	R′	R″
12	H	CH_3	H
13	H	CH_3	Cl
14	(S)-$CHCH_3C_6H_5$	OH	Cl

C=N plane) and steric repulsion of the o-hydrogen atoms of the two aromatic rings will, however, restrict free rotation and allow the presence of only few rotamers. The torsional angles found in the crystalline state range from 14° to 85° (positive and negative).[7–12] This situation is thus similar to that in benzophenones[16] which are also not coplanar.

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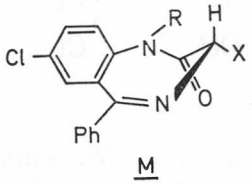
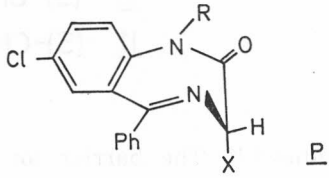
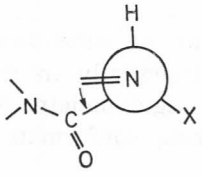
* In this homochirally analogue series replacement of the (3S)-alkyl-substituent by OH (**11**) does not change the configurational descriptor (**3S**) nor the conformational descriptor (**M**) along bond C-3/N-4; along bond C-2/C-3 it changes, however, formally to **P.**

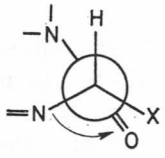


M



P





The chromophoric system of 1,4-benzodiazepin-2-ones has been compared with that of o-amino-benzophenon oxime[17,18] and the shifts of band position by different substituents have been discussed on this bases. UV and CD spectra of cross-conjugated chromophores can be described using simple Hückel theory[19] as being built up from two partial chromophores, viz. ring A plus the C=N moiety (chromophore A«), and ring C plus the same C=N group (»chromophore C«), which are strongly coupled because of the common azomethine group.

For partial chromophore A the position of the α- (B_{2u}-) and p-band (B_{1u}, conjugation band) are found at 312 and 249 nm[20], respectively. The maxima for the partial chromophore C should appear around 285 and 250 nm, and for a very similar compound these have been described to show up at 287/278 (B_{2u}) and 245 nm (B_{1u}).[21,22] The CD-spectrum of the model compound **33** gives a negative Cotton effect at 284 nm and a positive one at 247 nm, which is in perfect agreement with the data mentioned. The other two Cotton effects (218 nm and 199 nm, both negative) could come (at least in part) from the lactone chromophore. *p*-Substitution by fluorine (**34**) leaves the λ_{max}-values practically constant and enhances somewhat the rotational strength, however a *p*-bromo substituent shifts all CD-bands bathochromically. The cis-configurated hydrogenation product **36** gives a very small Cotton effect within the α-band with its usual fine structure, the next CD-band appears at 226 nm.

Although the transition moments for the excitations corresponding to these α-bands are appr. three times larger than for that of benzene as can be determined from the UV-spectra, these moments are still one order of magnitude too small to give rise to appreciable exciton coupling.[23] We assign, therefore, band I to the α-band of partial chromophore A, and band II will in part be due to the α-band of chromophore C and in part to an $n \rightarrow \pi^*$ transition of this same moiety, which is expected to give an absorption in the same range.[24] The excitations corresponding to the »conjugation bands« (*p*-bands, B_{1u}) of the two partial chromophores are associated with much stronger electric transition moments. These two bands are assigned to the broad and intense shoulders in the UV-spectrum of **2** around 240 to 255 nm and will give rise to a strong exciton couplet in the CD-spectrum (bands III and IV) because of the chiral arrangement of these transition moments. In a similar way both components of the E_{1u}-transition will also give rise to strong exciton coupling and could thus be responsible for the strongest UV-band around 233 nm and the CD-bands at shorter wavelengths, although they may still have other parentage.[25]

Such an approximation of the cross-conjugated chromophore in these compounds by a combination of two »local« chromophores sharing the C=N-group is, of course, only allowed, if the whole system is strongly twisted. Otherwise one has to discuss the MO-s of the full chromophore, and this will lead i. a. to the disappearance of the CD-couplet III/IV. The observed changes of the CD-spectra after protonation of the Schiff-bases (see later) might perhaps be explained in this way.

In order to apply successfully the exciton coupling theory one has to determine the direction of the transition moment vectors for both partial chromophores. They have been roughly estimated by Davidsson et al.[4], but this could be done in better approximation with the help of Platt's[29] or

Petruska's[30] spectroscopic moments (or »*q*-values«). Since that of C=N is not tabulated we had to calculate it from published UV-spectra, and obtained a value of appr. + 17 (on Petruska's scale;[30] Figure 2).

The uncertainty about the torsional angle around the C-5/C-1' bond does not matter as long μ is directed appr. along this same bond, as is estimated for the *p*-band (Figure 2). Also the fact that the »poles« actually developed

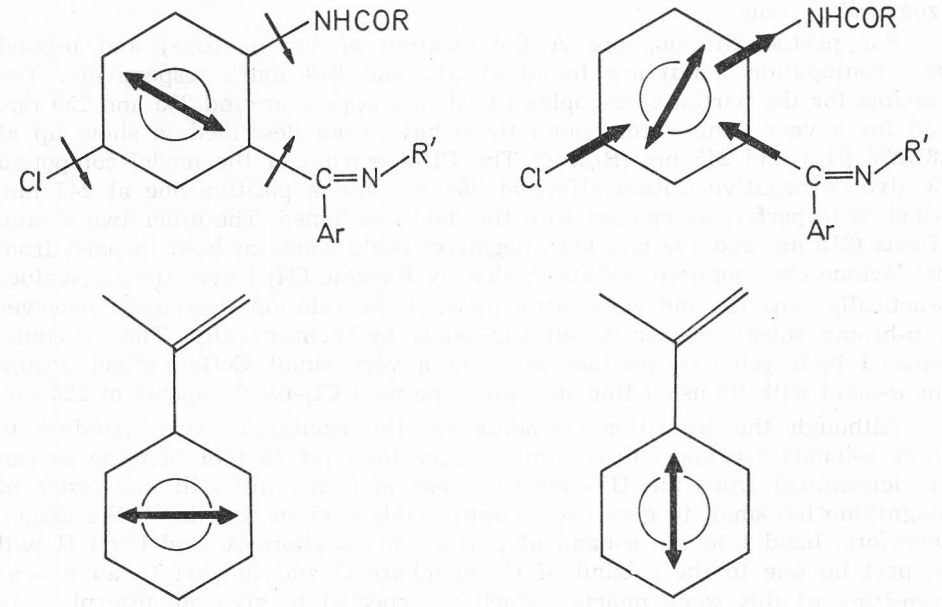


Figure 2. Approximate directions of the electric transition moment vectors for the B_{2u} (left) and B_{1u} (right) transitions within partial chromophore A (top) and C (bottom).

during excitation are localized appr. 0.8—1.0 Å above and below the benzene rings does not drastically change their Coulomb interaction for the possible geometries. For other directions of μ (e. g. for one component of the allowed E_{1u}-transition) magnitude and even the sign of the interaction potential will, however, strongly depend on the above mentioned torsional angle.

The two possible coupling modes (A and B) for the B_{1u}-transitions are depicted in Figure 3 together with the overall μ- and m-vector (the latter describing the charge rotation). The two moments are approximately antiparallel for the higher-energy coupling mode (A) and parallel for mode B (the relative energies of the excited states A and B are estimated by application of Coulomb's law). From this treatment follows that a »positive couplet« is expected for the absolute conformation present in **2** with (**3S**)-configuration, as is indeed formed by CD-bands III and IV. The negative wing (CD-band IV) is obviously to a great extent compensated by another strong positive CD at shorter wavelengths (CD-band V). This couplet is, however, of the usual »conservative« type for the corresponding compound **15**.

CD-bands I and II apparently also seem to form such a CD-couplet. As mentioned above the corresponding transition moment vectors are, however, too small to give rise to such a strong coupling. These two Cotton effects

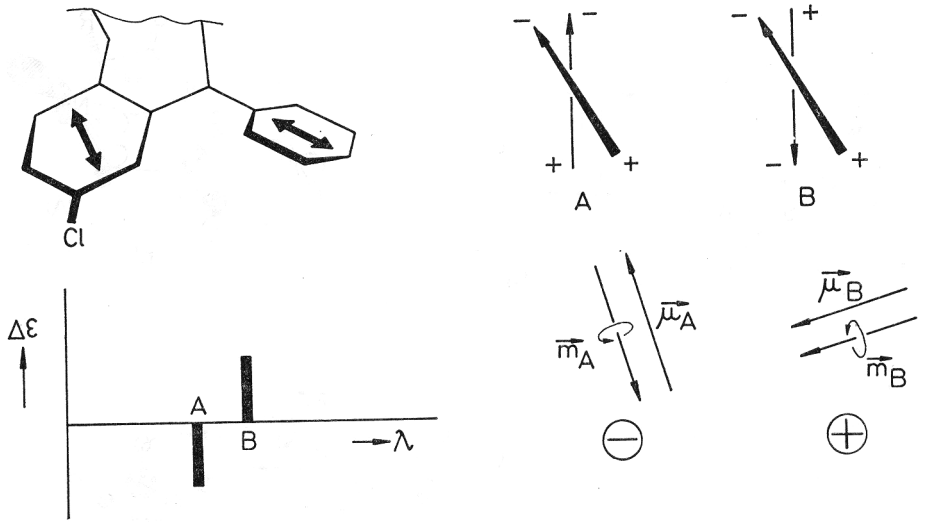


Figure 3. Exciton coupling of the B_{1u}-transition moments of chromophores A and C. The projection on the right is from chromophore C towards chromophore A. For A-mode (at higher energy) the sum electric transition moment is antiparallel to the magnetic transition moment created by the combined movements of electrons, the CD-sign is therefore negative. In B-mode (lower energy) the two vectors are parallel, the CD is positive. On bottom left a schematic representation of the expected CD-couplet is given.

must, therefore, correspond to individual absorptions. They are quite intense because both partial chromophores are inherently chiral. For such cases one can expect a g-value[31] ($g = \Delta\varepsilon/\varepsilon$) of appr. 10^{-2}, and for band I, which is rather isolated from the other Cotton effects, we found in the maximum $g = 3.10^{-3}$, which is still of the right order of magnitude.[25].

For partial chromophore A the direction of polarization of the B_{2u}-transition due to the presence of three substituents is directed appr. along the bond connecting ring A with the C=N moiety (Figure 2). This situation resembles to a great extent that of the *p*-band in a simple chiral styrene, and thus some conjugation with the C=N π-system is possible. For such a chromophore the correlation between absolute conformation and sign of the CD within this band is known.[32] A negative torsional angle between the double bond and the near half of the benzene ring gives rise to a positive CD. As we are dealing with $\pi \rightarrow \pi^*$-transitions the exchange of one carbon atom against nitrogen at the end of the chromophore should not dramatically alter this correlation. The respective torsional angle in **2** is $+45^0$, so a strong negative CD is expected, and this is indeed found for band I.

The direction of polarization for the α-band of chromophore C is also given in Figure 2. Together with the C=N (or with the whole partial chromophore A) this chromophore C is also inherently chiral. Because of the possibility of adopting conformations with positive and negative torsional angles, partial compensation of the produced Cotton effects is expected, which should make the CD for this transition smaller than for that of band I. We conclude, therefore, that CD-band II is mainly due to the first $n \rightarrow \pi^*$ transition of the conjugated azomethine chromophore which has small ε and whose absorption maximum should lie between 270 and 310 nm for chromophore A[24]. As the polarity of the 1,4-benzodiazepin-2-ones does not allow

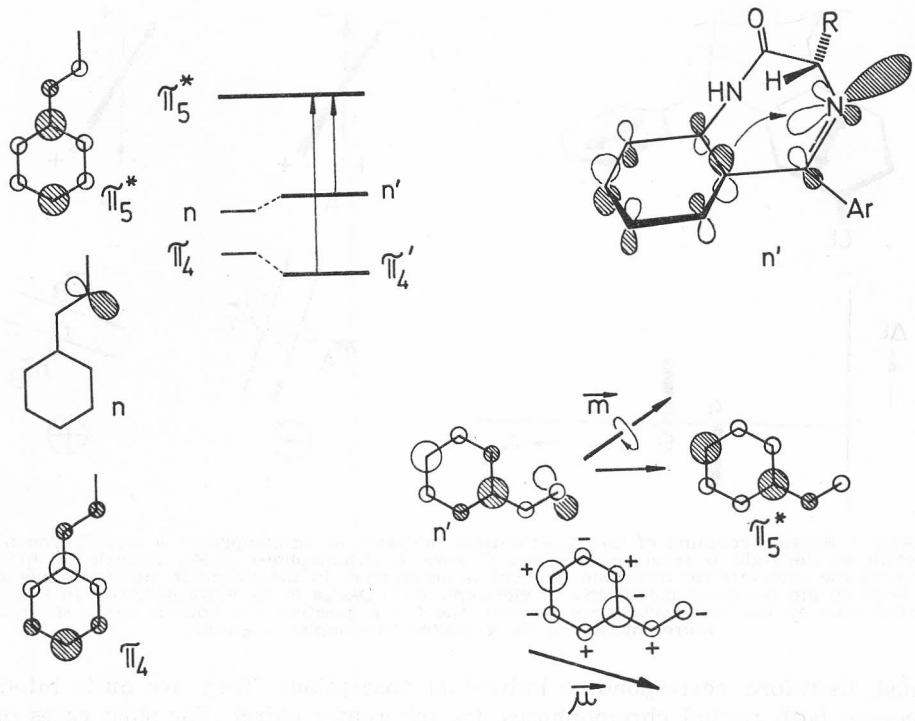


Figure 4. By the chirality of the system n- and π_4-MO of the chromophore A are not anymore strictly orthogonal and can mix. The new nonbonding orbital is n and has some π_4-character. The signs of the respective overlapping orbital lobes have to be opposite (cf. arrow in figure top right) and by this the relative phases are determined. The thus developed electric and magnetic transition moment vectors include an acute angle, the CD for the $n' \rightarrow \pi^*_5$-bands is, therefore, positive for the absolute configuration shown.[5]

measurements of their CD-spectra in unpolar solvents we had to run these spectra in acetonitrile (or ethanol) before and after the addition of a few drops of trifluoro acetic acid in order to identify the $n \rightarrow \pi^*$-transition. By this acidification both the CD- and the UV-spectra changed quite drastically. Most noteworthy is a large bathochromic shift (from 316 to 369 nm) for both the CD- and UV-band I of **2**. The formerly strong positive CD around 290 nm (band II) changes into a weakly negative one, the couplet (III/IV) collapses to a single (positive) Cotton effect, and a very intense CD-couplet appears in the short wavelength range. Obviously protonation at N-4 releases some strain in ring B which allows better conjugation and at the same time changes the geometry of the two transition moment vectors of the *p*-bands, so that they become less suited for exciton coupling. The observed change of sign of the CD around 290 nm can best be explained by assuming the disappearance of a strong positive $n \rightarrow \pi^*$ Cotton effect; what remains is the weak (negative) α-band CD of chromophore C.

This view is supported by the comparison of the CD-spectra of **34** in acetonitrile, before and after acidification. The originally negative Cotton effect around 285 nm (—1.45) becomes positive (+1.17). Thus the stronger negative $n \rightarrow \pi^*$ Cotton effect and the weaker positive α-band Cotton effect appear practically at the same wavelenght for chromophore C.

The sign of the CD for this $n \rightarrow \pi^*$ band of **2** can be estimated by application of qualitative MO theory in a similar way as has been done for non-coplanar conjugated enones[33] or simply by formal application of the corresponding rule for chiral 1-tetralones.[34] As ring C can adopt conformations with positive and negative torsional angles around the C-5/C-1' bond we can neglect its influence upon the *n*-orbital on nitrogen. Instead of using thus the full MO-s of a benzophenone typ π-system (which leads to the same result) we can rather work with the MO-s of the inherently chiral chromophore A alone. As is shown in Figure 4 this treatment leads to a positive sign for the $n \rightarrow \pi^*$ Cotton effect in case of **M**-conformation of ring B, and is thus in agreement with the measured positive CD-band II of **1** through **9** and **11**.

By this reasoning the sign of the first four Cotton effects I to IV can thus be non-empirically correlated with the absolute configuration of **2**.

That the CD of these benzodiazepines is indeed determined mainly by the chirality of the first sphere is nicely shown by a comparison of the Cotton effects of **11** and **14** (Figure 5).

Because of opposite chirality at C-3, ring B of **11** is the mirror image of that of **14**, the absolute configuration within the phenylethyl-amine (PEA) moiety is, however, the same in both compounds. **11** and **14** are, therefore, diastereomers, nevertheless their CD-spectra are nearly enantiomorphic to

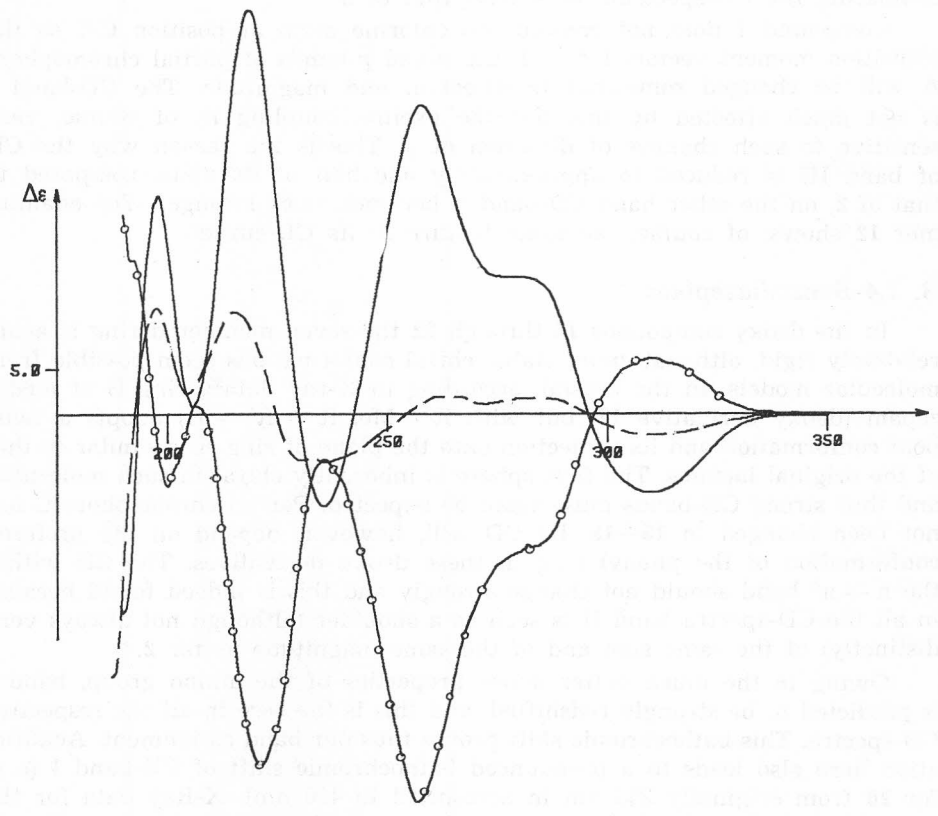


Figure 5. CD of **10** (- - - -), **11** (———), and **14** (—○—○—○—) in acetonitril solution.

each other as expected if only the inherently chiral system of rings A, B and C governs the chiroptical properties. The influence of the chiral substituent on N-1 can be studied with the help of **10** which lacks the chiral centre at C-3. Its CD-curve is similar to that of **2**, but the Cotton effects are smaller, and they become relatively weaker if one proceeds from short to long wavelengths (Figure 5). Whether the chiral side chain also changes the population ratio of the two ring conformations, or influences CD only by chirally perturbing the chromophoric systems, cannot be decided on the basis of these CD-spectra.

Compound **13**, the enantiomer of **2**, gives as expected a CD-spectrum which is the mirror image of that of **2**. Replacement of the methyl group by isopropyl (**3**), 1-hydroxyethyl (**4**), benzyl (**5**), or *p*-hydroxy-benzyl (**6**) does nearly not change the appearance of the CD-curve. Even the indole derivative **7** shows the same CD above 230 nm; at 223 nm there appears in this case a very strong CD, which must then come from a chiral interaction between the indole chromophore and the chromophoric system of the 1,4-diazepine-2-one moiety.

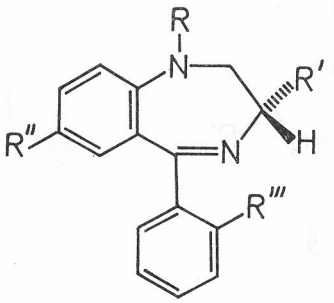
N-Methylation of **2**—**8** does not influence the CD-spectrum above 230 nm, as expected, the CD-maxima below 230 nm are, however, shifted all somewhat towards less positive or more negative values. A similar trend is found by comparing the CD-spectrum of **9** with that of **5**.

Compound **1** does not contain the chlorine atom at position C-7 so the transition moment vectors for both the α-and p-bands of partial chromophore A will be changed somewhat in direction and magnitude. The CD-band I is not much effected by this but the exciton coupling is, of course, very sensitive to such changes of direction of μ. This is the reason why the CD of band III is reduced to approximately one half of its value compared to that of **2**, on the other hand CD-band V becomes much stronger. The enantiomer **12** shows, of course, the same feature in its CD-curve.

B. 1,4-Benzodiazepines

In the deoxy compounds **15** through **22** the seven-membered ring is again relatively rigid, although more stable chiral conformations seem possible from molecular models. In the crystal, according to X-ray data[35], ring B of medazepam (deoxy derivative **12**, but with R = Me, R′ = R″ = H) adopts a twist boat conformation and its projection onto the plane of ring A is similar to that of the original lactams. The first sphere is inherently chiral in such molecules, and thus strong CD-bands must again be expected. Partial chromophore C has not been changed in **15**—**18**. Its CD will, however, depend on the prefered conformation of the phenyl ring in these deoxy derivatives. The CD within the $n \rightarrow \pi^*$ band should not change strongly and this is indeed found because in all the CD-spectra band II is seen as a shoulder (although not always very distinctly) of the same sign and of the same magnitude as for **2**.

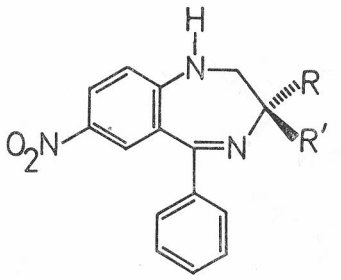
Owing to the much better donor properties of the amino group, band I is predicted to be strongly redshifted, and this is the case in all the respective CD-spectra. This bathochromic shift proves thus our band assignment. Acidification here also leads to a pronounced bathochromic shift of CD-band I (e. g. for **20** from originally 355 nm in acetonitril to 450 nm). X-Ray data for the medazepam hydrochloride[12] revealed only minor changes in the over-all geo-



	R	R′	R″	R‴
15	H	CH_3	Cl	H
16	H	C_2H_5	H	H
17	H	C_2H_5	Cl	H
18	CH_3	C_2H_5	Cl	H
19	CH_3	C_2H_5	Cl	F
20	CH_3	C_2H_5	Cl	Cl
21	C_2H_5	C_2H_5	H	H
22	C_2H_5	C_2H_5	Cl	Cl

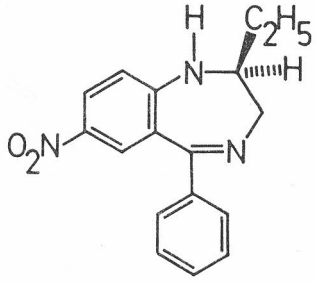
metry of the seven-membered ring, however. The directions and magnitudes of the transition moments of partial chromophore A are also somewhat changed by the replacement of the amide by the amine substituent, which obviously affects the short-wavelength bands more than the long-wavelength ones, because the typical exciton couplet III/IV is now much better developed (»conservative«). The rotational strength within IV resembles here that of III, the band which had compensated to a great extent CD-band IV in the 1,4-benzodiazepin-2-ones must thus be associated with another transition of the »acylamide chromophore« of **2**. As otherwise the CD-spectra of **17** and **2** are similar, the chiralities of the first spheres (and therefore also the absolute conformations of the seven-membered rings) must be the same for these two types of benzodiazepines. As in the case of the oxo-compounds the CD-couplet III/IV collapses after protonation; instead of the medium strong positive Cotton effect II, a weak negative CD (— 1.0 for **20**) appears around 292 nm, in agreement with the assignment of CD-band II as mainly coming from an $n \rightarrow \pi^*$-transition.

N-Methylation of **17** to **18** will mainly influence the conformation but barely change the transition moments, and its effect is seen in a blue shift and decrease of intensity of the CD-band I. The lone electron pair on the amine nitrogen obviously decreases its interaction with the π-system of ring A by



23 $R = C_2H_5$, $R' = H$

24 $R = H$, $R' = C_2H_5$



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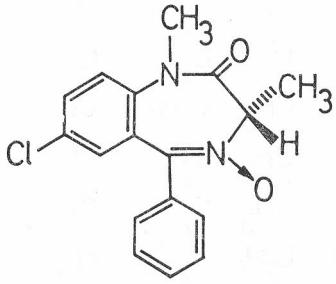


26

this conformational change. CD-Band II (shoulder) is slightly more intense, CD-bands IV and V decrease, however, appreciably in intensity.

Replacement of the chlorine atom of **17** by hydrogen (**16**) must bring about a small blue-shift of CD-band I, and this is observed. CD-band II with a positive sign and of the usual rotational strength, is more distinctly seen because CD-band III is also blue-shifted by 7 nm. The magnitude of the exciton couplet III/IV is, however, unchanged in agreement with the known fact[36] that a chlorine substituent has only a minor influence upon the p-band absorption.

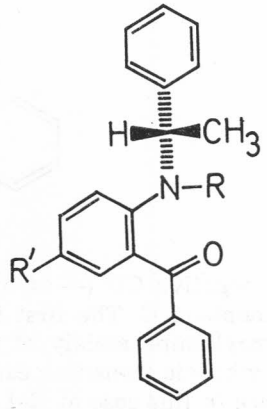
Exchange of methyl to ethyl at *N*-1 of 1,4-benzodiazepines inverts the sign of Cotton effect I to weakly positive for **21**, but leaves the CD-spectrum otherwise nearly unchanged. The CD-spectra of **22** and its methyl homologue **20** are, however, very similar to each other. In spite of this obvious inconsistency within CD-band I the absolute configuration of the *N*-1 ethyl derivatives of 1,4-benzodiazepines can unequivocally be determined from the strong Cotton effects at shorter wavelengths.

Finally, introduction of a fluorine or chlorine atom into the 2'-position of the phenyl ring C (**19**, **20**, **22**) should only weakly change the conformation of this ring and thus have only minor influence upon the α- and *p*-band

absorptions, whereas in the shorter wavelengths region more drastic changes can be expected. The CD-spectra are in agreement with these predictions. CD-band II can hardly be detected as a shoulder on the much stronger CD-band III but seems still to have the usual characteristic as judged from the width of CD-band III. The CD-spectra of the 7-nitro derivatives **23**—**25** differ completely from those of the related products **15**—**22** and this is expected because the nitro-group is a very strong perturber, and furthermore it has its own absorption bands. These spectra, as that of the N-oxide **26** are cited simply for comparison.

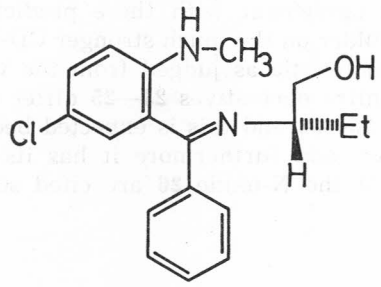
C. Related Model Compounds

The CD-spectra of the model compounds **33**—**36** have already been discussed above. Another model for the azomethine derivative of appropriately substituted benzophenones is **31**, which lacks the chiral ring B. Its Cotton effects are, therefore, one order of magnitude smaller than for the 1,4-benzodiazepines **15**—**22**, and the α-band CD of chromophore A appears here at even larger wavelengths, viz. around 370 nm. Other Cotton effects are at 281 nm ($n \rightarrow \pi^*$ and/or α-band of chromophore C), appr. 258 nm, 235 nm, around 213 nm, and at 203 nm. Because of the uncertainty of the C=N configuration and the possibility of many conformations a more detailed discussion of these bands seems premature.

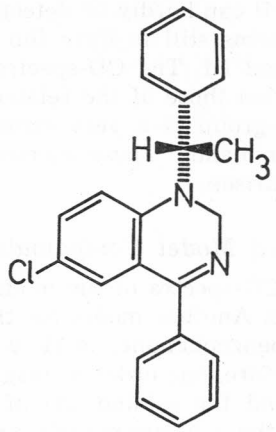


27 R=H, R′=Cl
28 R=CH_3, R′=Cl
29 R=$COCH_2Br$, R′=Cl
30 R=H, R′=NO_2

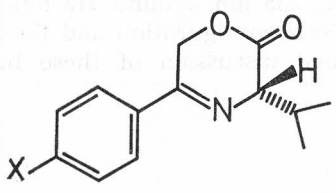
In best agreement with the above assignment of the bands are also the CD-spectra of the benzophenones **27**—**29**. The α-band CD of chromophore A appears e. g. for **27** at 400 nm and is quite intense (+ 6.5) for such an apparently flexible system. The $n \rightarrow \pi^*$ Cotton effect is also positive for this enantiomer (broad band around 340 nm), a negative CD is around 282 nm (p-band of



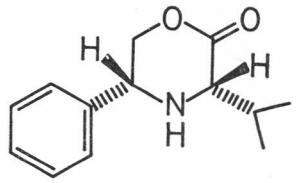
31



32



33 X=H
34 X=F
35 X=Br



36

chromophore A), and a strong negative CD (— 14 around 241 nm) could correspond to the p-band of chromophore C. The first fine structure band of the phenyl chromophore of the benzylamine moiety at 268 nm can be seen very distinctly, and even the second vibronic transition can be identified in this CD-spectrum. Protonation takes place in this case at N-1 (benzodiazepine notation!) and so no pronounced shift of the α-band (chromophore A) takes place, although the intensity of this Cotton effect decreases to appr. 20%. Then $n \rightarrow \pi^*$ Cotton effect acquires some fine structure in the same wavelength range (≈240 nm), which is even more pronounced for the amide **29**. The α-band CD of chromophore A is strongly shifted hypsochromically by such an amide formation (most probably the positive Cotton effect at 305 nm corresponds to it). It is interesting to note that the N-methylation of **27** to **28** inverts the sign of the first Cotton effect around 400 nm and also of the $n \rightarrow \pi^*$ Cotton effect. At shorter wavelengths the CD-bands are less pronounced, indicating thus much smaller g-values as for **27**. The CD-spectrum of the nitro derivative **30** is again cited only for comparison.

Model compound **23** contains a six-membered instead of the usual seven-membered ring B. This ring is also chiral and can adopt two enantiomeric

conformations. As can be judged from the relatively strong Cotton effects their energy difference in presence of the chiral ligand at *N*-1 is pronouncedly larger than for the seven-membered analogue **10**. CD-band I appears similarly as for the ketones **27** and **28** at 402 nm, and the Cotton effects at 282 nm (+ 7) and 244 nm (— 11) might correspond to the CD-couplet III/IV of the optically active benzodiazepines.

TABLE I

CD Data for the Compounds **1**—**36**

N⁰				
1	221.5/+36.1 318.0/+ 7.9	238.5/— 1.9	259.0/+36.9	283.5/— 8.3
2	198.0/+12.0 258.6/+32.5	205.0/— 2.4	220.6/+30.4	237.2/+ 2.5
3	198.2/+15.0 288.5/+ 5.3 (sh)	221.2/+37.1 316.2/— 7.6	238.2/— 3.2	260.2/+34.1
4	198.0/+ 9.6 259.0/+27.3	206.0/+ 0.4 275.0/+ 8.5	222.0/+28.4 285.0/+ 6.6	238.0/— 1.5 316.0/— 5.9
5	206.5/— 8.9 284.0/+ 8.4	222.5/+40.7 291.0/+ 5.4	241.0/— 3.0 316.0/— 6.8	259.5/+25.7
6	205./0— 6.2 284.0/+ 8.4	225.0/+45.6 316.0/— 7.9	240.0/+ 7.2	260.0/+27.4
7	225.0/+105.0 293.5/+ 5.2	240.5/—30.9 317.0/— 8.2	260.0/+29.2	284.0/+ 7.6
8	197.0/+ 4.2 261.0/+28.4	208.0/—10.7 280.0/+ 4.6	224.0/+11.9 290.0/+ 4.2	237.0/— 3.4 318.0/— 7.3
9	187.0/—39.4 240.0/+ 0.9 318.0/— 7.6	199.0/+ 4.0 263.0/+36.2	207.0/—10.3 280.0/+10.3	223.0/+32.2 289.0/+ 9.4
10	197.6/+11.9 261.6/+ 1.7 310.6/— 2.2	215.0/+11.4 266.4/+ 1.8	230.0/— 5.2 283.8/+ 1.7	235.4/— 5.4 284.2/+ 1.7
11	198.2/+24.3 281.0/+15.3	218.6/+45.2 310.0/— 8.8	235.4/—10.3	257.8/+34.5
12	187.0/+75.7 255.0/—20.8	203.0/+10.6 277.0/— 9.0 (sh)	223.0/—44.4 306.0/+ 8.4	243.0/+ 7.3
13	199.0/— 0.9 260.0/—19.9	205.0/+ 7.4 270.0/—13.4 (sh)	222.0/—23.4 315.0/+ 6.1	238.0/+ 6.5
14	200.8/— 8.0	220.8/—39.2	256.6/—43.4	310.0/+ 6.2
15	187.4/—71.6 267.0/+25.8	199.4/+11.6 305.0/+ 2.9 (sh)	220.5/+38.4 355.8/— 2.7	241.0/—22.9
16	188.0/—87.6 260.0/+24.6	200.0/— 3.8 289.0/+ 6.3	219.0/+62.4 347.0/— 2.6	239.0/—32.1
17	189.0/—83.9 241.0/—32.3	200.0/+11.6 268.0/+30.4	206.0/+ 1.9 359.0/— 2.8	221.0/+43.9
18	199.2/+27.9 345.0/— 1.3	220.4/+35.8	240.0/—12.1	268.6/+35.2
19	204.0/+45.7 344.0/— 0.4	220.4/+19.9 449.2/+ 0.01	243.0/—21.3	279.0/+29.9
20	187.4/—51.5 275.8/+27.2	203.3/+15.1 352.2/— 1.2	220.2/+17.3	240.9/—26.6

Table I continued

21	180.0/—55.8 238.0/—15.7	200.0/+ 8.5 263.0/+33.5	205.0/+ 5.9 356.0/+ 0.2	217.0/+52.5
22	188.8/—51.2 227.8/+24.4	204.4/+ 9.1 280.4/+26.5	220.6/+13.0 348.0/— 0.4	240.6/—29.8 419.8/+ 0.01
23	188.0/—24.0	200.4/+ 6.3	298.0/+ 2.7	385.2/+ 2.7
24	187.0/+56.5 270.0/+ 1.3	204.0/— 9.9 300.0/— 4.2	217.0/—18.3 331.0/+ 0.2	239.0/+ 9.6 385.2/+ 2.7
25	190.0/— 6.7 238.0/— 2.5	198.0/+ 6.1 389.0/+ 1.8	203.0/+ 2.7	218.0/+ 8.5
26	186.0/+29.1 285.0/+ 1.5	202.0/+15.6 (sh) 3.22.0/— 2.6	245.0/+ 2.1	265.0/— 7.4
27	240.6/—13.8 401.7/+ 6.4	265.4/— 0.4	269.0/+ 0.4	324.0/+ 0.8
28	194.3/+ 8.4 208.4/— 5.5 230.3/+ 1.1 270.2/— 4.2	198.7/— 3.7 216.2/+ 1.4 233.6/+ 1.0 295.6/+ 0.2	204.5/— 5.4 220.3/+ 2.2 236.3/+ 0.9 384.8/— 1.2	206.7/— 5.6 224.2/+ 1.8 238.6/+ 0.8
29	213.8/+19.0 338.0/+ 0.2	236.2/— 4.8 352.6/+ 0.2	260.4/— 1.7 368.6/+ 0.1	305.2/+ 0.3
30	192.2/+35.5 367.8/+ 4.1	210.8/— 3.6 379.4/+ 4.2	213.7/— 4.6	269.9/+ 2.6
31	188.6/—13.4 277.0/+ 0.9	202.8/+ 1.7 368.6/+ 0.2	214.4/+ 1.4 386.4/+ 0.1	234.8/— 4.1
32	204.8/+ 1.9 401.0/+ 2.4	221.4/+ 1.8	243.6/—10.9	280.8/+ 7.1
33	199.0/— 2.3	218.0/— 2.6	248.0/+ 4.4	284.0/— 2.9
34	282.6/— 1.4	286.6/— 1.5	319.6/— 0.05	320.6/— 0.05
35	196.0/— 3.3	222.0/— 3.3	254.0/+ 5.9	288.0/— 3.8
36	227.0/+ 1.9	261.0/+ 0.1	267.0/+ 0.1	

EXPERIMENTAL

All CD-spectra were recorded with an ISA dichrographe Mark III at room temperature in cells from 0.10 to 2.00 cm path length and at concentrations of appr. 1 mg/ml (in acetonitrile).

Preparations

General remarks. Melting points were determined on a Kofler microheating stage (Boetius), and are not corrected. IR spectra (KBr pellets) were obtained with a Perkin Elmer M 297 spectrophotometer (only strong bands are indicated). NMR spectra were run on a Perkin Elmer R 12 intrument with TMS as an internal standard; shifts are given in δ-scale downfield from TMS. Optical rotations were measured on a Perkin Elmer 141 polarimeter at ambient temperature. Thin layer chromatography (TLC) was performed on alumina plates precoated with Merck silica gel 60 F 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.

Compounds **1**—**9**, **12** and **13** are prepared as described in the ref. 5, compound **26** as in reference 6, compounds **10**, **11**, **14**, **27**, **29** and **30** are described in the ref. 38, and compounds **33**—**36** as in ref. 39, compound **15** is described in a forthcoming paper.[40]

(S)-3-Ethyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine (**16**)

2-Amino-benzophenone (9.85 g, 0.05 mol) was dissolved in S-(+)-2-amino-butanol (90 ml) and 1.0 g of 2-methylimidazol hydrochloride was added. The mixture was heated under reflux for 8 hrs, then the excess of the reagent was evaporated in vacuo, residual oil was slurried in water (200 ml), and extracted with ethylacetate (3 × 100 ml). Organic extracts were dried, evaporated and crude hydroxyethyl-imine dissolved in polyphosphoric acid methyl ester, (PPM, 150 g) preheated to 80 °C. After 4 hrs heating at 90—100 °C the reaction mixture was cooled, and ice-water (300 g) was added. The resulting suspension was filtered, filtrate was made alkaline with conc. ammonia, and crude **16** which precipitated was extracted with benzene (3 × 150 ml). Organic extracts were dried, and evaporated affording crude product (10.4 g), which on crystallization from diisopropylether melted at 86—88 °C. $[\alpha]_D = +228^0$. The unit of the specific rotation is 10^{-1} deg cm^2 g^{-1} (c = 1.05 in $CHCl_3$). IR: 3220, 2960, 2920, 2850, 1620, 1485, 1355, 1320, 1240, 755, 745, 698 cm^{-1} NMR($CDCl_3$): 1.06 (t, 3H); 1.5—2.2 (m, 2H); 3.6 (broad s, 3H); 3.85 (broad s, 1H, NH); 6.5—7.8 (m, 9H).

Anal. for $C_{17}H_{18}N_2$ (250.37) calc'd.: C 81.56; H 7.25; N 11.19%
found: C 81.42; H 7.07; N 10.90%.

(S)-3-Ethyl-5-(o-fluorophenyl)-7-chloro-1-methyl-2,3-dihydro-1H-1,4-benzodiazepine (**19**)

Starting from 2-amino-5-chloro-2'-fluorobenzophenone (24.95 g, 10.0 mmoles), and S-(+)-2-amino-butanol (35 ml), intermediary β-hydroxyethyl-imine has been prepared as described for **16**. The crude product was cyclised in 30 g of PPM during 6 hrs at 80—90 °C. After work-up as described for **16** crude **19** (14.9 g, 47% overall yield) was crystallized from 2-propanol affording pure product with m. p. 120—121 °C. $[\alpha]_D = +332^0$ (c = 1.58 in $CHCl_3$). IR: 2965—2860 (m), 1610, 1482, 1447, 1492, 880, 820, 758 cm.$^{-1}$ NMR ($CDCl_3$): 1.00 (t, 3H); 1.5—2.1 (m, 2H); 2.80 (s, 3H); 3.1—3.4 (m, 3H); 6.7—7.8 (m, 7H).

Anal. for $C_{18}H_{18}ClFN_2$ (316.81) calc'd.: C 68.24; H 5.72; N 8.85%
found: C 68.48; H 5.94; N 8.90%.

(S)-3-Ethyl-1-methyl-5-(o-chlorophenyl)-7-chloro-2,3-dihydro-1H-1,4-benzodiazepine (**20**)

Compound **20** was obtained starting from 2-amino-5-chloro-2'-chlorobenzophenone (4.0 g, 15.0 mmol) and S-(+)-2-amino-butanol (55 ml) as described for **19**. Crude product (1.7 g, 34%), was crystallized from 2-propanol affording pure material with m. p. 95—97 °C. $[\alpha]_D = +190.3^0$ (c = 1.94 in $CHCl_3$). IR: 2950, 2850, 1620, 1500, 1460, 1380, 1320, 1295, 1245, 1195, 1125, 1073, 1050, 1040, 892, 820, 775, 753, 715 cm.$^{-1}$ NMR ($CDCl_3$): 1.00 (t, 3H); 1.5—2.1 (m, 2H); 2.80 (s, 3H); 3.1—3.4 (m, 3H); 6.7—7.6 m, 7H).

Anal. for $C_{18}H_{18}Cl_2N_2$ (333.25) calc'd.: C 64.87; H 5.45; N 8.40%
found: C 64.78; H 5.27; N 8.62%.

(S)-3-Ethyl-1-ethyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepine (**21**)

2-Ethylamino-benzophenone (1.97 g, 10.0 mmole), and S-(+)-2-amino butanol (30 ml) were heated under reflux in the presence of 0.2 g of 2-methylimidazol hydrochloride for 6 hours. The intermediary hydroxyethylimine was isolated as described for **16**. It was dissolved in 20 ml of polyphosphoric acid ethylester (PPE), and heated at 160 °C under vigorous stirring, and in a nitrogen atmosphere for 8 hours. The mixture was allowed to cool to ambient temperature, ice-water (100 g) was added, and undissolved impurities were filtered off. The filtrate was made alkaline by addition of conc. ammonia, and crude **21** which precipitated was extracted with benzene (3 × 100 ml). Dried organic exstracts were evaporated, and crude product was crystallized from diisopropylether, affording 1.34 g (48% overall yield) of pure **21**, m. p. 62—65 °C. $[\alpha]_D = +226^0$, (c = 1.00 in $CHCl_3$). IR: 2940, 2855, 1615, 1585, 1520, 1370, 1312, 1290, 1190, 1120, 1065, 1030, 770 cm.$^{-1}$ NMR ($CDCl_3$): 1.00 (t, 3H); 1.12 (t, 3H); 1.5—2.1 (m, 2H), 2.82 (q, 2H); 3.0—3.45 (m, 3H); 6.6—7.5 (m, 8H).

Anal. for $C_{19}H_{22}N_2$ (278.40) calc'd.: C 81.97; H 7.97; N 10.06%
found: C 81.80; H 7.59; N 9.88%.

(S)-3-Ethyl-1-ethyl-5-(o-chlorophenyl)-7-chloro-2,3-dihydro-1H-1,4--benzodiazepine (**22**)

Starting from 2-ethylamino-5-chloro-benzophenone compound **22** has been prepared in strictly the same way as described for 21. Crude **22** (39% overall yield) was crystallized from diethylether-acetone affording pure product with m. p. 89—90 °C. $[\alpha]_D = +176.4^0$ (c = 2.08 in $CHCl_3$). IR: 2960, 2900, 1610, 1510, 1385, 1295, 1055, 890, 815, 775, 720 $cm.^{-1}$ NMR ($CDCl_3$): 1.00 (t, 3H); 1.12 (t, 3H); 1.6—2.1 (m, 2H); 2.95 (q, 2H); 3.0—3.5 (m, 3H); 6.7—7.5 (m, 7H).

Anal. for $C_{19}H_{20}N_2Cl_2$ (346.39) calc'd.: C 65.89; H 5.81; N 8.09%
found: C 65.66; H 6.02; N 8.14%.

2-N-(S)-α-Phenylethyl-N-methylamino-5-chloro-benzophenone (**28**)

2-N-(S)-α-Phenylethylamino-5-chloro-benzophenone[37] (500 mg, 1.48 mmol), and hexamethylentetramine (800 mg) were heated under reflux in toluene (15 ml) for 2 hours. Thereafter 0.1 ml of trifluoroacetic acid, and sodium borohydride (200 mg) were added and heating under reflux proceeded for another 4 hours. Then water (20 ml) was slowly added, organic layers separated and aqueous phase extracted with toluene. Organic extracts were dried, evaporated and residual oil was purified on a silicagel column. Compound **28** was obtained in the first fractions as a yellow oil (120 mg), which was purified by distillation, m. p. 95—100 °C/0.1 mmHg. IR: 3060, 3015, 2990, 1660, 1595, 1490, 1475, 1455, 1392 $cm.^{-1}$ NMR ($CDCl_3$): 1.45 (d, 2H); 2.32 (s, 3H); 4.38 (q, 1H); 6.7—8 (m, 13H).

Anal. for $C_{22}H_{20}ClNO$ (349.85) calc'd.: C 75.52; H 5.76; N 4.00%
found: C 75.63; H 5.37; N 3.95%.

(S)-(+)-2-Methylamino-5-chlorobenzophenon-β'-hydroxy-α'-ethyl-ethylimin (**31**)

2-Methylamino-5-chlorobenzophenone (20.0 g, 81.5 mmol), S-(+)-2-amino-butanol (80 ml), and 1 g of 2-methylimidazol hydrochloride were heated under reflux for 6 hours. The excess of reagent was evaporated in vacuo, oily residue was slurried in water (0.5 l), and extracted with benzene (3 × 100 ml). Dried organic extracts were evaporated to dryness, and the crude product was repeatidly crystallized from ether affording 13.9 g (54%) of pure **31**, m. p. 87—89 °C. $[\alpha]_D = -5.9^0$ (c = 1.02 in $CHCl_3$). IR: 3400, 1620, 1600, 1575, 1525, 1470, 1380, 1245, 1120, 1060, 1045, 985, 910, 890, 815, 810, 765, 705 $cm.^{-1}$. NMR ($CDCl_3$): 0.80 (t, 3H); 1.4—2.0 (m, 2H); 2.0—3.8 (m, 7H); 6.4—7.6 (m, 8H); 9.8 (broad s, 1H).

Anal. for $C_{18}H_{21}ClN_2O$ (316.82) calc'd.: C 68.30; H 6.71; N 8.82%
found: C 68.22; H 6.52; N 8.59%.

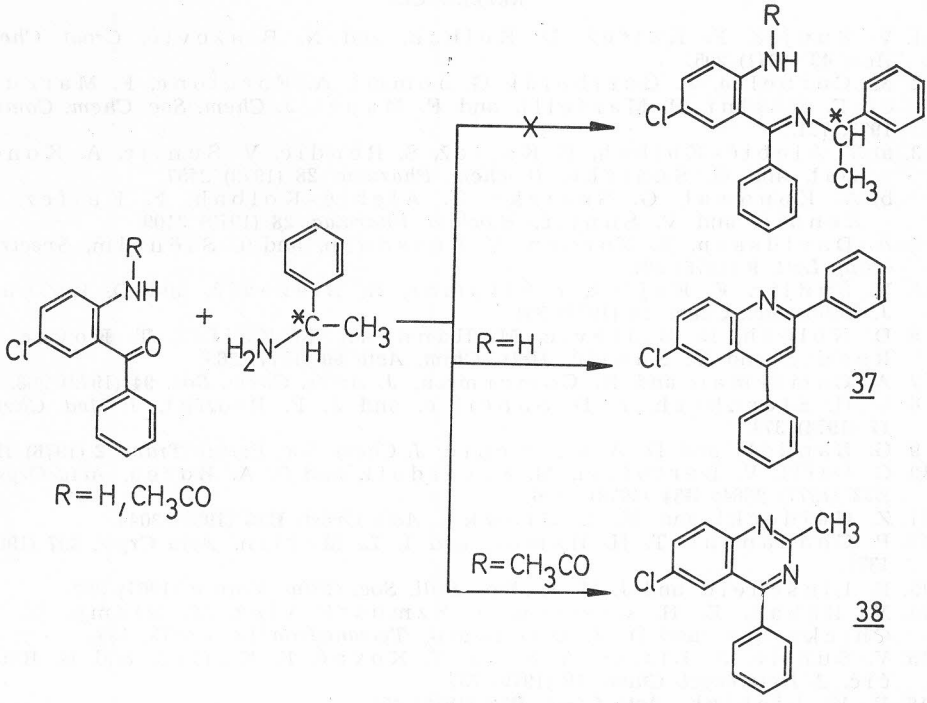
1-(S)-α-Phenylethyl-4-phenyl-6-chloro-1,2-dihydro-quinazolon (**32**)

Chromatographic purification of **28**, as described earlier, afforded as the second fraction pure compound **32**, which on crystallization from ether melted at 100—101 °C. $[\alpha]_D = +76.2^0$ (c = 1.10 in $CHCl_3$). IR: 2310, 1610, 1550, 1485, 1462, 1415, 1255, 900 $cm.^{-1}$ NMR ($CDCl_3$): 1.65 (d, 3H); 4.82 (s, 2H); 5.0 (q, 1H); 6.8—8 (m, 13H).

Anal. for $C_{22}H_{19}ClN_2$ (346.84) calc'd.: C 76.18; H 5.52; N 8.07%
found: C 76.45; H 5.24; N 8.13%.

It is interesting to note that the attempts to prepar another type of chiral benzophenon-imines as the open-chain chiral models for benzodiazepines under investigations, according to the Scheme 1, failed. Instead, quinoline derivative **38** was isolated when the reactions were performed under harsh conditions. Formation of **37** presumably was accomplished via elimination of ammonia, and subsiquent ring closure, where an activated methyl group and a carbonyl group reacted. To form **38**, the intermediary benzophenon-imin must undergo intramolecular displacement of the phenylethygroup.

SCHEME 1.



2,4-Diphenyl-7-chloro-quinoline (**37**)

2-Amino-5-chloro-benzophenone (7.5 g, 32.5 mmol) and S-(—)-α-phenylethylamine (3.93 g, 32.5 mmol) were stirred and heated at 200 °C (oil bath) during 20 hours. The mixture was allowed to cool to ambient temperature, methanol (30 ml) was added, and ice-cooled overnight. The crude product which separated (7.1 g, 68%) was recrystallized from methanol affording pure **37** with m. p. 131—132 °C. IR: 1590, 1570, 1535, 1480, 1445, 1380, 1360, 1150, 1075 cm.$^{-1}$ NMR ($CDCl_3$): 7.2—8.4 (m, 14H).

Anal. for $C_{21}H_{14}ClN$ (322.82) calc'd.: C 79.87; H 4.47; N 4.44%
found: C 79.39; H 4.48; N 4.04%.

2-Methyl-4-phenyl-6-chloro-quinazoline (**38**)

2-N-Acetylamino-5-chloro-benzophenone (273 mg, 1.0 mmol) and S-(—)-α-phenylethylamine (120 mg, 0.11 mmol) were heated under stirring in 5 ml of HMPTA during 20 hours. Thereafter the mixture was cooled, ice-water (100 ml) added, and aqueous phase extracted with ether (3 × 50 ml). Dried organic extracts were evaporated and the crude product isolated on silica gel column (35 g) with diisopropylether as eluant. Thus 90 mg (35.5%) of the pure **38** was obtained m. p. 105—107 °C. IR: 1610, 1570, 1550, 1480, 1450, 1420, 1390, 1375, 1355, 1335, 1280, 1250 cm.$^{-1}$ NMR ($CDCl_3$): 2.98 (s, 3H); 7.6—8.2 (m, 8H).

Anal. for $C_{15}H_{11}N_2Cl$ (254.72) calc'd.: C 70.75; H 4.35; N 11.00%
found: C 70.69; H 4.14; N 10.82%.

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REFERENCES

1. V. Šunjić, F. Kajfež, D. Kolbah, and N. Blažević, *Croat. Chem Acta* **43** (1971) 205.
2. M. Corbella, P. Gariboldi, G. Jommi, A. Forgione, F. Marcucci, E. Musini, P. Martelli, and F. Mauri, *J. Chem. Soc. Chem. Comm.* 1973, 721.
3. a) T. Alebić-Kolbah, F. Kajfež, S. Rendić, V. Šunjić, A. Konował, and G. Snatzke, *Biochem. Pharmac.* **28** (1979) 2457.
   b) A. Konował, G. Snatzke, T. Alebić-Kolbah, F. Kajfež, S. Rendić, and V. Šunjić, *Biochim. Pharmac.* **28** (1979) 3109.
4. Å. Davidsson, B. Norden, N. Roosdorp, and I. Sjöholm, *Spectroscopy Lett.* **9** (1976) 301.
5. V. Šunjić, F. Kajfež, I. Štromar, N. Blažević, and D. Kolbah, *J. Heterocycl. Chem.* **10** (1973) 591.
6. D. Kolbah, N. Blažević, M. Hannoun, F. Kajfež, T. Kovač, S. Rendić, and V. Šunjić, *Helv. Chim. Acta* **60** (1977) 265.
7. A. Camerman and N. Camerman, *J. Amer. Chem. Soc.* **94** (1972) 268.
8. L. H. Sternbach, F. D. Sancilio, and J. F. Blount, *J. Med. Chem.* **17** (1974) 374.
9. G. Bandoli and D. A. Clemente, *J. Chem. Soc. Perkin Trans.* **2** (1976) 413.
10. G. Gilli, V. Bertolasi, M. Sacerdoti, and P. A. Borea, *Acta Cryst.*, **B33** (1977) 2664; **B34** (1978) 2826.
11. Z. Gałdecki and M. L. Głowka, *Acta Cryst.* **B36** (1980) 3044.
12. P. Chananout, T. H. Hamor, and I. L. Martin, *Acta Cryst.* **337** (1981) 1371.
13. P. Linscheid and J. M. Lehn, *Bull. Soc. Chim. France* (1967) 992.
14. M. Raban, E. H. Carlson, J. Szmuszkovicz, G. Slamp, C. G. Chickester, and D. J. Duchamp, *Tetrahedron Lett.* 1975, 139.
15. V. Šunjić, A. Lisini, A. Sega, T. Kovač, F. Kajfež, and B. Ruščić, *J. Heterocycl. Chem.* **16** (1979) 757.
16. B. W. Liebich, *Acta Cryst.* **B32** (1976) 431.
17. P. Grammaticakis, *Bull. Soc. Chim. France,* 1953, 93.
18. P. Levillain, M. Bertucat, and B. Perrot, *Eur. J. Med. Chem.*, **10** (1975) 433.
19. E. Hückel, *Z. Physik,* **70** (1931) 204; **72** (1931) 310; **76** (1932) 628.
20. A. Sabljić, unpublished results. Values are taken from the UV spectrum (in ethanol) of 5-methyl-7-chloro-3H-1,4-benzodiazepin-2(1H)-one.
21. a) T. Kubota, M. Yamakawa, and Y. Mori, *Bull .Chem. Soc. Japan,* **36** (1963) 1552; b) T. Kubota and M. Yamakawa, *Bull. Chem. Soc. Japan* **36** (1963) 1564.
22. E. Haselbach and E. Heilbronner, *Helv. Chim. Acta* **57** (1968) 16.
23. S. F. Mason, *Quart. Rev.* **17** (1963) 20.
24. c.f. e.g. D. Pitea and G. F. Favinin, *J. C. S. Perkin II* 1980 849.
25. S. D. Allen and O. Schnepp, *J. Chem. Phys.* **59** (1973) 4547.
26. S. F. Mason, in *Optical Rotatory Dispersion and Circular Dichroism,* G. Snatzke (Ed.), London, Heyden & Son, (1967) p. 71.
27. J. A. Schellman, *Acc. Chem. Res.* **1** (1968) 144.
28. M. Koreeda, N. Harada, and K. Nakanishi, *J. Amer. Chem. Soc.* **95** (1974) 266.
29. J. R. Platt, *J. Chem. Phys.* **19** (1951) 263.
30. J. Petruska, *J. Chem. Phys.* **34** (1961) 1111, 1120.
31. S. F. Mason, *Mol. Phys.* **5** (1962) 343.
32. P. Crabbé, *Chem. and Ind.* (London), 1969, 917, and references cited therein.
33. G. Snatzke, *Angew. Chem.* **91** (1979) 380.
34. G. Snatzke, M. Kajtár, and F. Snatzke, in F. Ciardeli and P. Salvadori (Eds.): *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism,* Heyden & Son, London (1973), p. 148.
35. G. Gilli, V. Bertolasi, M. Sacerdoti, and P. A. Borea, *Acta Cryst.* **B34** (1978) 3793.

36. H. H. Jaffé and M. Orchin, *Theory and Applications of Ultraviolet Spectroscopy*, Wiley, New York, 1962, p. 257.
37. V. Šunjić, M. Oklobdžija, A. Lisini, A. Sega, F. Kajfež, D. Srzić, and L. Klasinc, *Tetrahedron* **35** (1979) 2531.
38. M. Mihalić, V. Šunjić, P. Mildner, and F. Kajfež, *Croat. Chem. Acta* **48** (1976) 125.
39. V. Čaplar, A. Lisini, F. Kajfež, D. Kolbah, and V. Šunjić, *J. Org. Chem.* **43** (1978) 1355.
40. E. Decorte, R. Toso, T. Fajdiga, A. Sega, V. Šunjić, A. Lisini, *J. Heterocycl. Chem.*, in press.

SAŽETAK

Cirkularni dikroizam optički aktivnih 1,4-benzodiazepina

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Provedeno je iscrpno označavanje CD-vrpci derivate 1,4-benzodiazepin-2-ona (**1—14, 16**) ,te njihovih 2-deokso srodnika (**15—25**) koristeći kvalitativnu MO teoriju i teoriju sprezanih ekscitona. Nađeno je da vrpca kod najveće valne duljine (oko 310 nm), kao i ona kod 250 nm predstavlja B_{2u} i B_{1u} prelaz hiralnog »djelimičnog kromofora« A, dok su odgovarajuće vrpce za »djelimični kromofor« C označene kod 278—287 nm i oko 245 nm (Sl. 2.—4.). CD-predznaci za niz Cottonovih efekata mogli su biti određeni neempiričkim načinom. 7-Nitro derivati **23—25** nisu podlijegali ovoj analizi budući da je nitro skupina snažno ometajuća, a ujedno posjeduje vlastite apsorpcione vrpce u istom području. Pripravljeni su modelni ciklički i aciklički spojevi **27—36**, i njihovi CD-spektri analizirani na jednak način.