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CIRCULAR DICHROISM AND ABSOLUTE CONFIGURATION OF CHIRAL PHENYL-PHENYLAMINO-METHANES

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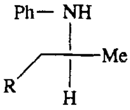
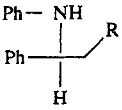
Abstract - The CD-spectra of 20 phenyl phenylamino methanes and of 2 model compounds are presented. From some of these it was concluded that the absolute configuration assigned before in the literature was incorrect and this has been proved by an X-ray diffraction study of **8**. The absolute configuration of **10** and **11** could be assigned from their very similar CD-spectra. All other compounds had already been chemically correlated with **8**, **10**, or **11**. The CD-spectra are not simply sum-curves of those of the two individual chromophores. Most of them can be explained by the assumption of exciton interaction between their respective p-bands. For **17** to **22** several conformations seem to be possible according to molecular models and no safe CD-correlation can, therefore, be done.

1. INTRODUCTION

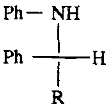
In the course of our synthetic and stereochemical studies on ß-amino acids and their derivatives we prepared a series of optically active compounds bearing an anilino (through the N-atom) and a phenyl chromophore at the same C-atom. Compounds **8**, **10**, and **11** were obtained by reaction of benzylidene aniline with the (-)-menthyl esters of 2-methyl propanoic, cyclopentanecarboxylic, and cyclohexanecarboxylic acids, respectively in the presence of $NaNH_2$ at -15°C. Under these conditions the reaction proceeds, however, only with low diastereoselectivity. On the other hand, by partial recrystallization in all three cases only one of the two possible diastereomers could be isolated in optically pure state[1,2]. The phenylamino propanols **5**, **6**, and **7** were obtained by LAH reduction of **8**, **10**, and **11**,[2] while their stereospecific cyclization in the presence of i-PrMgBr afforded the

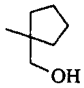
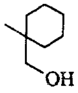


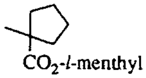
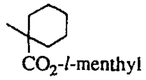
	R
1a	CO_2H
1b	CO_2Me
2	OH

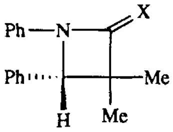


	R
3	H
4	OH

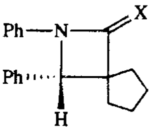


	R
5	$-C(Me)_2CH_2OH$
6	
7	

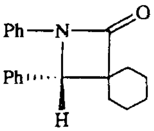
	R
8	$-C(Me)_2CO_2$-*l*-menthyl
9	$-C(Me)_2CONH_2$
10	
11	



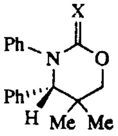
	X
12	H_2
13	O



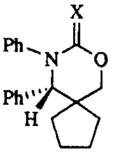
	X
14	H_2
15	O



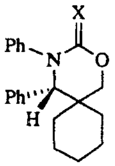
16



	X
17	H_2
20	O



	X
18	H_2
21	O



	X
19	H_2
22	O

corresponding 2-azetidinones **14**, **15**, and **16**.[1,2] The azetidines **12** and **13** were obtained from **5** and **6**, respectively by tosylation in pyridine.[3] The tetrahydro-1,3-oxazines **17** to **19** resulted by stereospecific Eschweiler-Clark cyclization from the propanols **5** to **7**, respectively[3]. The same propanols gave with phosgene in toluene the tetrahydro-1,3-oxazin-2-ones **20** to **22**.[3]

The absolute configuration of the model compound **1**[4] is known, and so is that of the starting materials for **2**, **3**, and **4**.[5,6] The absolute configuration of all other compounds were, however, uncertain. Furukawa et al.[7] had proposed for the free acid corresponding to **10** an absolute configuration which could not explain our CD-results, and therefore we had undertaken an X-ray analysis, which was obtained from **10**. This showed indeed that this previous assignment, which had still been used in our previous work[1,2], was incorrect.

2. CIRCULAR DICHROISM

The phenyl-phenylamino-methanes **3** to **22** contain both the aniline and the phenyl chromophore bonded to the same centre of chirality and we might, therefore, expect an interaction between them. The chiroptical properties of chiral phenyl derivatives are quite well known and we have ourselves investigated extensively several simple types[4,8-11]. Not so much is known, however, about the aniline chromophore, and we discuss, therefore, first the CD of those 3 model compounds which we had at hand (**1a**, **1b**, and **2**).

Table 1. UV-Data of **1** to **5**

No.	Solvent[a]	max(ϵ)
1a	I	290(1420), 244(8200), 205(7900)
1b	I	290(2400), 244(13700), 202(18800)
2	E	295(1660), 250(10050)
3	E	300(2160), 248(17600)
4	E	295(2310), 245(16900)
5	E	300(2200), 250(13200)

[a] E: ethanol; I: isooctane

CD of **1a**, **1b**, and **2**. The UV-spectrum of a simple N-substituted aniline derivative like **1** or **2** shows the α-band at 290-295 nm (band II, ε ≈ 2000) and the p-band (IV) around 247 nm (ε ≈ 10 000) (Table 1). In the CD-spectrum (Table 2) two Cotton effects appear approximately at these same wavelengths, and two other ones can be detected around 255 nm (III) and near 222 nm (V). A very weak additional Cotton effect (I) between 310 to 315 nm is barely detectable. The $|\Delta\epsilon|$-values of these Cotton effects are all below 1. Empirically we further note that for these compounds which have always hydrogen, Me, aniline and a (substituted) aliphatic group around the centre of chirality the (*S*)-configuration leads to a negative CD within bands I, III, and V, whereas that of band II and IV is positive (cf. CD of **5**, Figure 1). The solvent (isooctane, acetonitrile) influences somewhat the magnitudes of these CD-bands, but not their signs. CD-band I can best be detected for **2**, in whose spectrum on the other hand CD-band II is much smaller than in the other spectra, so they may both belong to the same transition and indicate the presence of different conformations.

CD of anilines containing an additional phenyl ring (**3** to **22**).

Compound **3** is built up from (*S*)-phenyl ethylamine and aniline and its CD-spectrum should look like the sum curve of that of the mentioned amine and of **2**, if no interactions take place, but this is obviously not the case (cf. Table 2). Even larger is the deviation from additivity for compounds **8** to **11**. Interestingly enough, below 230 nm the CD-curves of **3** and **8** to **11** are very similar to the sum curves of the individual components. It is worthwhile to note that formally **3** and **4** are derived from (*S*)-phenyl ethylamine, all the others from its (*R*)-isomer. That nevertheless **4** obtains the designator (R)- and all the others (**3**, **5** to **22**) are named (*S*)-compounds is a consequence of the unequivocal Cahn-Ingold-Prelog rules.[12]

For **3** the MM2-calculation predicts the global energy minimum for the torsional angle around the (Ph-)N-C*(-Ph) bond as -76°, the relevant torsional angles around the bonds from this moiety to the (C-Ph) and the (N-Ph) bonds as -42° and +6°, respectively. Such a conformation would lead to a negative CD-couplet from the interaction of the two p-band transition moments, whose first wing is expected to appear at a somewhat longer wavelength than that of the corresponding UV-maximum, which is at 248 nm. The negative Cotton effect at 253 nm could thus well be the first wing of the mentioned couplet. The second wing is

Table 2. Circular Dichroism of compounds **1** to **22**

No.	Solvent[a]	[$\lambda_{max}(\Delta\epsilon)$]
1a[4]	A	293(+0.48), 260(-0.29), 240(+0.8), 218(-0.6)
1b[4]	A	295(+0.51), 257(-0.27), 241(+0.4), 219(-0.7)
2[6]	A	311(-0.04), 290(+0.08), 254(-0.3), 238(+0.1), 224(-0.2), 214(+0.2), 200(-1.3)
3[6]	A	316(+0.02), 288(-0.51), 272sh(-0.43), 253(-3.5), 224(+1.3), 212(-5.0), positive at shorter wavelengths
4[6]	A	290(-0.55), 269(+0.03), 252(-2.7), 228sh(+0.7), 223sh(0.9), 210(-4.1), positive at shorter wavelengths
	A+H$^+$	290(-0.01), 274(-0.02), 268(+0.21), 261(+0.19), 214(-1.9)
5[2]	A	297(+2.81), 253(+4.92), 225(-1.1), 213(+4.2), 202(-6.8)
	A+H$^+$	298(+0.22), 269(-0.11), 256(+0.31), 217(+5.7), 213(+8.0), 208(+6.8), 192(+38.2), negative at shorter wavelengths
	E	298(+3.18), 270(-0.46), 252(+5.16), 225(-0.6), 213(+6.3)
	E+H$^+$	297(+1.68), 254(+2.68), 213(+9.9), negative at shorter wavelengths
	D	298(+3.08), 270(-0.42), 253(+5.48), 214(+8.2), negative at shorter wavelengths
6[2]	A	299(+3.00), 256(+5.02), 226(-1.1), 214(+6.5), 203sh(-10.5), 190(-83.7),
	A+H$^+$	296(+0.26), 268(-0.23), 250(+0.22), 222(-3.0), 214(+2.6), 192(+42.5)
7[2]	A	299(+2.53), 257(+5.20), 226(-1.2), 214(+8.0), 204sh(-8.8), 192(-65),
	A+H$^+$	300(+0.93), 256(+1.80), 222(-1.4), 214(+3.1), 192(+39)
8[1]	A	294(+3.30), 249(+5.47), 222(-2.1), 213(+4.1), 202(-6.5)
	A+H$^+$	292(+2.08), 249(+4.7), 223(-2.0), 213(+10.1), 203(-3.6), 196(+5), negative at shorter wavelengths
	D	294(+3.30), 269(-0.45), 250(+5.1), 223(-1.8), 213(+2.6), negative at shorter wavelengths
9[1]	A	296(+1.92), 253(+2.3), 213(+4.2), 200sh(-4.6)
	D	298(+2.76), 270(-0.68), 255(+2.2), 234sh(+0.6), 213(+7.2), negative at shorter wavelengths
10[2]	A	295(+2.94), 249(+5.52), 223(-2.2), 213(+4.2), 201sh(-13.4), 190(-84)
	A+H$^+$	296(+1.13), 248(+2.7), 225(-0.6), 212(+8.8), 194(+15), negative at shorter wavelenghts
11[2]	A	296(+3,31), 269(-0.44), 250(+4.9), 224(-2.7), 215(+6.1), 202sh(-15.7), 191(-80.)
	A+H$^+$	297(+1.93), 243(+4.2), 214(+8.7), 196(+12), negative at shorter wavelenghts
12[3]	A	295sh(+0.50), 274sh(+0.68), 252(+6.7), 217(+3.7), 202 (-1.2), 197(+2), negative at shorter wavelengths
	D	275sh(+0.58), 251(+7.2), 217(+5.9)
13[3]	A	290sh(+0.71), 252(+8.2), 217(+5.9), 204(-7.1), 195(+19), negative at shorter wavelengths
14[1]	A	282(-0.44), 277sh(-0.28), 268sh(+1.52), 245(+9.7), 223sh (+2.9), 209(-4.9), 199(+2.0), 192(-11)
	D	284(-0.28), 278sh(-0.18), 247(+10.2), 211(-2.4)
15[2]	A	284(-0.29), 270sh(+2.68), 245(+11.5), 209(-7.1), 191(-47)
16[2]	A	284(-0.26), 269sh(+1.89), 245(+11.0), 210(-10.8), 192(-50)

Table 2 continued

No.	Solvent[a]	[λ_{max} ($\Delta\epsilon$)]
17[3]	A	291(+0.17), 248(-11.9), 222(+2.9), 209sh(-13.2), 197(-30)
	A+H$^+$	291(+0.03), 250(-2.1), 211(-12.4), 197(-19), positive at shorter wavelengths
	D	289(+0.23), 247(-16.6), 223(+6.2)
18[3]	A	300sh(+2.13), 288(+3.32), 273sh(-4.90), 245(-9.9), 213sh (-24.7), 196(-117), positive at shorter wavelengths
19[3]	A	300sh(+0.32), 291(+0.36), 268sh(-2.10), 244(-9.1), 209sh (-17.5), 196(-63)
	A+H$^+$	295(+0.03), 259sh(-0.87), 252(-0.9), 212(-11), 198(-12), positive at shorter wavelengths
20[3]	A	272(-0.29), 265(+0.17), 260(-0.14), 226(-8.2), 222sh(-7.8), 213(-8.1), 194(+7), negative at shorter wavelengths
	D	274(+0.15), 269(-0.23), 266(+0.06), 262(-0.33), 227sh (-10), 215(-12.3), positive below 205 nm
21[3]	A	273(+0.37), 265(+0.23), 261(-0.18), 227(-12.2), 214(-13.2), 192(+109), negative at shorter wavelenghts
22[3]	A	273(+0.34), 266(+0.22), 261(-0.15), 227(-10.8), 214((-10.6), 191(+103), negative at shorter wavelenghts

[a] The CD-spectra were recorded on a ISA-Dichrograph Mark III, connected on-line to a PDP-8/E at room temperature. The concentrations were appr. 10^{-4} molar.

[b] A: acetonitril, D: dioxane, E: ethanol.

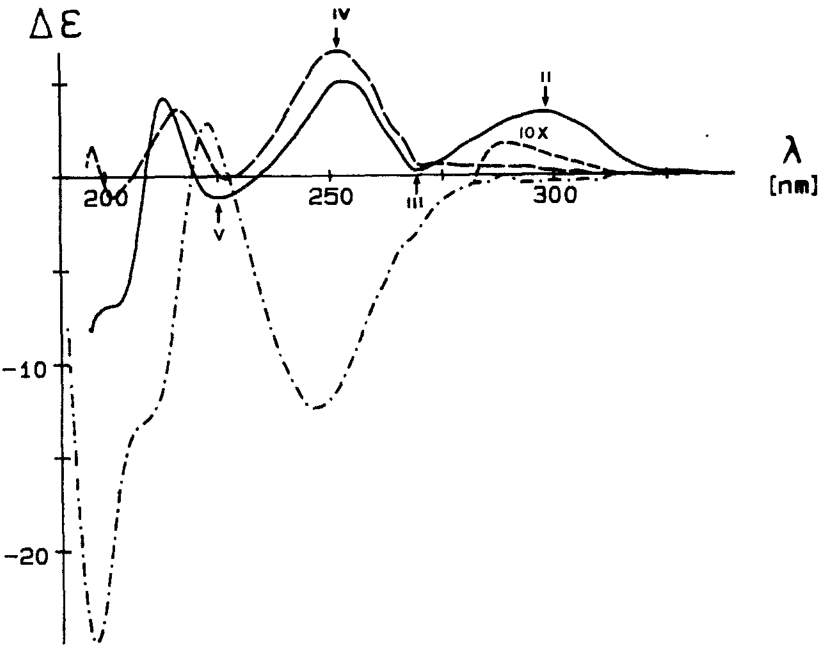


Fig. 1. CD spectra of 5 (——), 12 (---), and 17 (-.-.-) in acetonitrile and band assignment (II-V).

expected to show up around 210 - 215 nm, which could, however, already be overcompensated by another strong CD at this short wavelength. For **4** in a solvent which is not breaking internal hydrogen bonds the conformation of the whole molecule is rigidified with the C(-NH) and C(-CH_2OH) bonds approximately coplanar. Also for this conformation a negative CD-couplet is predicted for the same interaction as discussed for **3**, and indeed we found here a negative CD at 252 nm in acetonitrile. The $\Delta\epsilon$-value is rather small for an exciton couplet, which can be due *e.g.* to the presence of other conformations in solution. Such a hydrogen bond will be broken by protonation of the nitrogen, and at the same time the anilino chromophore looses its typical character and gives spectra like toluene.[13] The CD-spectrum of **4** after acidification shows indeed between 250 and 300 nm the usual small Cotton effect with pronounced fine structure lines at 268 and 261 nm. These positions agree well with those for a monoalkylated benzene.[9]

The structure of **5** is similar to that of **4** with one more bond between the centre of chirality and the HO-group. This CH_2OH group is, however, flanked by two *gem*-dimethyl groups and therefore sterically rather hindered. For the (*S*)-enantiomer a medium strong positive Cotton effect is observed within bands II and IV, a band I can no longer be identified, band V is definitely negative, and so must be band III, which in some solvents is however present only as a positive minimum (Figure 1). At still shorter wavelengths at least two more Cotton effects are visible, *viz*. a positive one around 213 nm, and a negative one around 200 nm. These CD-spectra are very similar in acetonitrile, ethanol or dioxan as solvent. Addition of a drop of acid to the solution deminishes all Cotton effects to different extents, depending on the solvent, and the typical toluene lines around 270 nm can also be observed.

The origins of bands II and IV have already been discussed, band III must then correspond to the α-band of the phenyl group. A hydrogen bond from the HO- to the amino group is now in a six-membered ring and so the torsional angles around the relevant bonds must deviate from those of **4**. Still one predicts from the models a negative CD-couplet, if one assumes the same absolute configuration as given in ref.[1,2,7], whereas its first wing at 253 nm is positive, as is the CD of band II. Even if we were not dealing here with CD-couplets still the Cotton-effects of **4** and **5** between 350 and 220 nm are enantiomorphous to each other and rose doubt about the absolute configuration of **5** and the other related compounds. Therefore an X-ray diffraction measurement was done with **8**,[14] which compound contained the menthyl-moiety of known absolute configuration. The originally assigned absolute configuration[7] indeed turned out to be incorrect. The absolute configuration of **5**, therefore, must be (<u>S</u>).

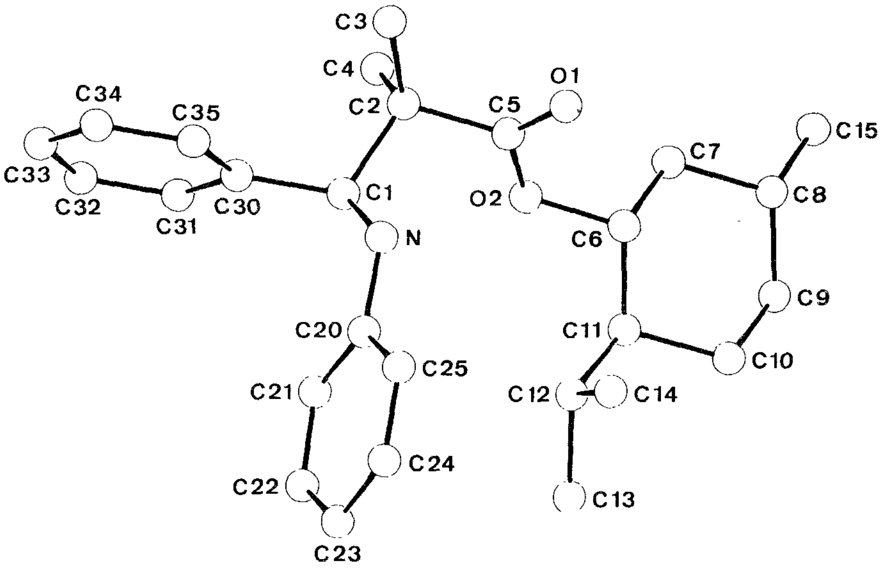


Fig. 2. Moleculare structure, atomic numbering scheme and selected geometrical data of **8**:
N - C1 1.455(4), C1 - C2 1.555(4), C2 - C5 1.533(4), C5 - O1 1.189(4)Å,
N - C1 - C2 109.7(2), C1 - C2 - C5 107.0(2), C2 - C5 - O2 111.0(3)°

The CD-spectra of **6** to **11** are all very similar to each other and to that of **5**, although the magnitudes of the individual Cotton effects vary somewhat. Therefore all these compounds must have the same absolute configuration. Since some of these do not contain the HO-group their preferred conformation cannot be due to such a mentioned hydrogen bond, but in all cases the NH-group could act as donor as well. This does, however,not change the arguments given above.

A four-membered ring as it is present in **12** and **13** is in general not planar. As is also well known from X-ray diffraction data in an aniline derivative the nitrogen atom is somewhat pyramidalized. Taking these facts together and releasing the 1:2 strain within the Ph-N-C-Ph moiety the torsional angle between the two long axes of the aromatic rings is appr. +100° to +130°. This arrangement will again lead to a positive CD-couplet. CD-band IV is positive with a $\Delta\epsilon$-value of more than 5 for both compounds, so this is in agreement with the prediction. Actually the CD of these compounds with a very rigid four-membered ring was the reason for casting doubt onto the originally assumed absolute configuration.

In the CD-spectra of the lactames **14** - **16** some sharp lines are found between 270 to 290 nm, and these are characteristic for the α-band of the acetanilide chromophore. Band IV is rather strong ($\Delta\epsilon$ up to +10) and this is a good indication that we are indeed dealing with a CD-couplet, which has the same sign as for **12** and **13**. Since the N-acylation barely changes the direction of the long-axis transition moment the observed sign of this couplet is again in agreement only with the revised but not with the originally proposed absolute configuration. Near 225 nm a very distinct positive shoulder can be observed which might correspond to the $n\text{->}\pi^*$ transition of the ß-lactame chromophore.[15]

For the oxazines **17** - **19** a weak but distinct Cotton effect could be observed between 290 to 310 nm, which must be associated with the α-band absorption of the anilino moiety. A CD-band corresponding to such absorption of the phenyl unit cannot be detected in these spectra. The Cotton effect between 245 - 250 nm is negative and quite strong. If the assumption is correct that this is again the first band of a CD-couplet than it follows from its sign that the torsional angle between the two long axis is negative. NMR-evidence advocated for an equatorial conformation of the phenyl ring[3] but does not give further details. In such a heterocyclic six-membered ring slight deformations are easily possible and could lead to a negative torsional angle for the diphenyl moiety.

As expected, for the three oxazinones **20** - **22** the fine structure within the two α-bands is more pronounced and we note 3 to 5 lines in the respective wavelengths range of bisignate character. The p-band of the phenylurethane chromophore gives a quite strong negative CD around 225 - 230 nm, which might therefore be the first wing of a negative CD-couplet. According to NMR studies[3] the C-phenyl group is preferably axially arranged, but since the solvents and concentrations used for both measurements differ appreciably we must not have the same conformations preferred during the CD- and the NMR-experiment. From the CD we can only conclude that the torsional angle between the two long axes of the two phenyls is negative, too.

In summary we could give a consistent explanation of the CD-spectra of phenyl-phenylamio methanes in which the main stereochemical arguments rest on the assumption of exciton coupling between the two aromatic π-systems. This led to the suspicion that the absolute configuration of these compounds proposed previously in literature was incorrect. Later X-ray diffraction measurements could indeed confirm this. In a few cases with compounds containing a more flexible heteroring CD is not conclusive for the unequivocal assignment of the absolute configuration because of ambiguities of the ring conformation.

ACKNOWLEDGEMENTS

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REFERENCES

1. St.Christoskova, E.Simova, B.Kurtev, a.*Colloque Franco-Bulgare*, Tryavna, **1980**, 250, b.Ann.Univ.Sofia **1980**, *74*, 115
2. St.Christoskova, E.Simova, B.Kurtev, *C.r.Bulg.Acad.Sci*.**1981**, *34*, 1509
3. St.Christoskova, E.Simova, B.Kurtev, *C.r.Bulg.Acad.Sci*. **1982**, *35*, 661
4. K.Netzke, Thesis Bochum (1987)
5. B.Kurtev, E.Simova, M.Victorova, N.Berova, St.Christoskova, *Mh. Chem*. **1981**, *112*, 669
6. St.Christoskova, N.Berova, E.Simova, St.Spassov, B.Kurtev, G.Snatzke, *Proc. FECS Int.Conf.on CD, Sofia, Sept. 21-25*, **1985**, *6*, 315
7. M.Furukawa, T.Okawara, H.Noguchi, Y.Terawaki, *Heterocycles* **1977**, *6*, 1323
8. W.Schoenfelder, G.Snatzke, *Isr.J.Chem*. **1980**, *20*, 142
9. N.Berova, B.Kurtev, G.Snatzke, *Tetrahedron* **1983**,*39*, 1371
10. N.Berova, B.Kurtev, G.Snatzke, *Croat.Chem.Acta*, **1985**, *58*, 189
11. K.Netzke, G.Snatzke, *Chem.Ber*. **1989**, *122*, 1365
12. V.Prelog, G.Helmchen, *Angew.Chem*. **1982**, *94*, 614
13. H.Suzuki, *Electronic Absorption Spectra and Geometry of Organic Molecules,* Academic Press, New York **1967**, 222
14. Crystal data of **8:** Formula $C_{27}H_{37}NO_2$, mol wt 407.6 $gmol^{-1}$, orthorombic, $P2_12_12_1$, a = 6.224(1), b = 9.915(1), c = 40.125(2)Å, V = 2476.2$Å^3$, Z = 4,d_{calcd} = 1.09 gcm^{-3}, = 1.54178Å, μ = 4.92 cm^{-1}, F(000) = 888, T = 20°C, Enraf-Nonius CAD4 diffractometer, scan mode ω- 20, $(\sin\theta/\lambda)_{max}$ = 0.63 $Å^{-1}$, 3988 reflections measured ($\pm$h, +k, +l), 3828 unique reflections, 3311 observed reflections [$I>2\sigma(I)$], solution by direct methods, all hydrogen atoms were calculated and kept fixed during refinement, 271 refined parameters, R = 0.053, R_w = 0.037, EOF = 5.73.
    Atomic coordinates, thermal parameters, bond lengths and angles are available on request from the Cambridge Crystallographic Data Centre.
15. H.Rehling, H.Jensen, *Tetrahedron Lett*. **1972**, 2793.