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OPTICAL ACTIVITY OF LACTONES AND LACTAMS—II

CHIROPTICAL PROPERTIES OF 4-OXAZOLIDINONES

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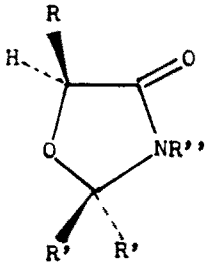
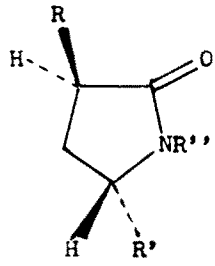
Abstract—Several optically active 4-oxazolidinones were obtained from amides or N-methylamides of corresponding α-hydroxy acids. The influence of solvent and substituent on their CD was studied. The predominance of the envelope conformation was established for these compounds, the degree of puckering being enhanced by polar solvents. The folded form with the aromatic ring facing the oxazolidinone ring was observed for 5-benzyl substituted oxazolidinone derivatives.

Lactone and lactam chromophores can be treated as systems derived from the carboxylate anion[1-3] and comparison of their chiroptical properties appears very fruitful.[1-6] Unfortunately, only few examples of lactones and lactams with the same dissymmetric molecular framework are known.[2,5,6] 1,3-Dioxolan-4-ones and 4-oxazolidinones, the heterocyclic analogues of γ-lactones and γ-lactams respectively, with the same side chains seem to be proper models for such comparisons. In the preceding paper chiroptical properties of 1,3-dioxolan-4-ones were described.[7] The present studies are directed at oxazolidinones with unequivocal absolute configuration obtained from amides of α-hydroxy acids.[8,9]

Several optically active compounds **1–5** were obtained in acid catalyzed reaction of (S)-α-hydroxy acid amides or N-methylamides with paraformaldehyde or corresponding ketones. The ring geometry of 4-oxazolidinones is governed by similar factors as for 1,3-dioxolan-4-ones.[7] Analogously to γ-lactams,[10] the envelope conformation (A), with amide group, C-2 and C-5 atoms planar, and O-1 atom deviated from the ring plane, is the most preferred (Fig. 1). The ring chirality is determined by steric effect of bulky 5-substituent. The planar conformation B more strained than A is also possible. The existence of conformations with non-planar amide group is rather problematic. Since the C–O bond is shorter than C–C bond the 2,5-transannular interactions should play fundamental role for determining ring conformation. However, conformational analysis in case of 4-oxazolidinones is complicated by vicinal interactions of C-2 and N-3 substituents. The bulky groups at C-2 should cause flattening of the A form.





1a, R = Me; R′ = H; R″ = Me
1b, R = Me; R′ = Me; R″ = H
1c, R = Me; R′ = Et; R″ = H
2a, R = i-Pr; R′ = H; R″ = Me
2b, R = i-Pr; R′ = Me; R″ = H
2c, R = i-Pr; R′ = Me; R″ = Me
3a, R = i-Bu; R′ = H; R″ = Me
3b, R = i-Bu; R′ = Me; R″ = H
4a, R = Ph; R′ = H; R″ = Me
4b, R = Ph; R′ = Me; R″ = H

5a, R = CH_2Ph; R′ = H; R″ = Me
5b, R = CH_2Ph; R′ = Me; R″ = H
6, R = Me; R′ = H; R″ = H
7a, R = H; R′ = CH_2CO_2H; R″ = H
7b, R = H; R′ = CH_2CO_2H; R″ = Me

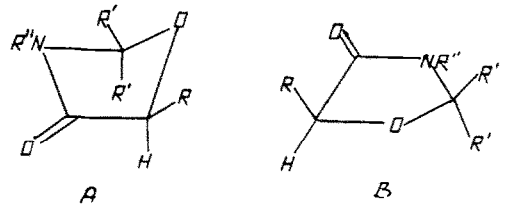


Fig. 1. Conformations of 4-oxazolidinones.

These predictions can be verified experimentally by CD if one can assign the Cotton effect (CE) sign for each conformation. For stereochemical correlation of lactam CE sign several rules have been developed.[3] According to the first one, the sign of CD for $n \rightarrow \pi^*$ transition of lactams is governed by the chirality of lactam ring.[11,12] Schellman and coworkers have proposed a quadrant rule for the peptide chromophore,[13] applicable also to lactams. More general rules explaining the chiroptical properties of both lactones and lactams have been worked out by Weigang *et al.*[1,2] According to this approach an octant rule is applicable for the lactam chromophore, which is treated as perturbed carboxylate ion. Some spherical distortion of the yz plane causes that the chiral ring gives the main contribution to CD. Weigang's sector rule gives positive CE sign for A and negative for B conformation of 4-oxazolidinones (Fig. 2). It is evident that these signs are opposite to those of 1,3-dioxolan-4-ones, since the sector signs for lactones are reversed to those for lactams.

The CD data for 4-oxazolidinones are collected in Table 1. The positive CD for **1–4** suggests the predominance of envelope A form in conformational equilibrium. The magnitude of CE increases with increasing solvent polarity, explained by enhanced puckering of A form in polar media. The influence of substituents on conformational equilibrium is more complicated than in 1,3-dioxolan-4-ones case. The CD magnitude slightly varies, when the 5-substituent bulkiness changes (compounds **1a–3a**) since the conformations other than A give a minute contribution to the equilibrium.

Comparison of the spectra for **1a–1c** reveals that the CD decreases along with increased size of the 2-substituent. This is a result of 2,3-interactions, which destabilize form A according as predicted. The remarkable effect of such interactions is also known for other types of lactams.[12,14] The different behaviour is observed for compounds **2a–2c**; the magnitude of CE increases when the substituent becomes larger. The preponderance of 2,5- over 2,3-interactions in such crowded compounds can serve as possible explanation. The strong magnitude of CE exhibited by **3c** may suggest the distortion of N-methyl group from ring plane. Such distortion cannot significantly raise energy of amides, as demonstrated by CNDO/2 calculations.[15,16]

The chiroptical properties of 5-phenyl-substituted compounds are very similar to those of related 1,3-dioxolan-4-ones. Compounds **4a** and **4b** exhibit weak CD near 260 nm, which can be assigned unequivocally to the ^1L_b transition, and intense CD near 220 nm, which corresponds to the $n \rightarrow \pi^*$ transition of homoconjugated β,γ-unsaturated amide chromophore.[7] The comparison of spectra of **4a** and **4b** shows that substitution of hydrogens at C-2 by methyl groups causes about three times enhancement of CD. This is a result of hindered rotation of the phenyl group, brought about by this substitution. Since non-polar solvents cause flattening of the oxazolidinone ring, then conformation A becomes more crowded, rotation of phenyl is more difficult, and the CD of **4b** increases in going from methanol to cyclohexane solution.

Some interesting observations provide the spectra of 5-benzylsubstituted 4-oxazolidinones (**5a** and **5b**). Besides of ^1L_b band at 260 nm, **5a** reveals negative CD in $n \rightarrow \pi^*$ region, in contrast with compounds with aliphatic side chains. According to the earlier predictions, the negative CE sign corresponds to the planar B conformation. What reasons are responsible for the preference of this strained conformation? The answer comes from 2,5-piperazinedione (diketopiperazine) stereochemistry. It is well established that phenylalanine and related diketopiperazines exist in folded conformation, in which the aromatic ring faces diketopiperazine ring.[17,18] This is a relatively unfavourable boat conformation of the ring in which the benzyl group occupies a flagpole position.

Inspection of Dreiding models points to close analogy between **5a** and phenylalanine diketopiperazine. The formation of folded form of **5a**, in which phenyl ring lies directly over oxazolidinone ring calls for axial or bisectional position of 5-benzyl substituent (Fig. 3), and then **5a** shows negative CE sign. NMR confirms existence of such form; both protons at C-2 show the same chemical shift (δ4.8) for 4-oxazolidinones with aliphatic side chains, but **5a** exhibits two signals at (δ4.30) and (δ4.65), because *cis*-proton is more shielded by phenyl ring than *trans*-proton. The substitution of C-2 hydrogens by methyl groups makes interaction between phenyl and heterocyclic rings difficult and then a small contribution of the form with aromatic ring lying away from the oxazolidinone ring can be expected. The five-membered ring exists therefore in A conformation, 5-benzyl takes pseudoequatorial position and positive CD appears at 233 nm. Since polar solvents favor A form the intensity of this band is greater in methanol than in cyclohexane solution.

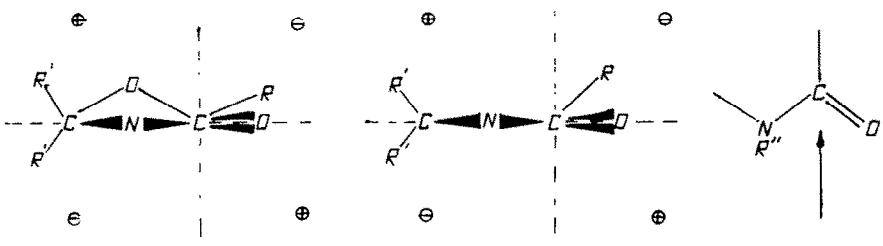
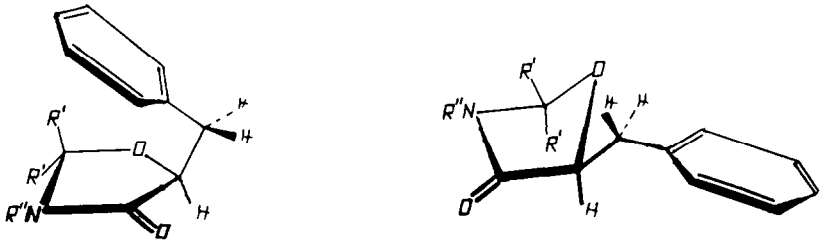


Fig. 2. Sector projections of 4-oxazolidinone conformations. The arrow shows the direction of projections.

Table 1. CD data for 4-oxazolidinones ([θ] in deg mole^{-1} cm^2, λ in nm)

Comp.	Solv.[a]	λ_{max}	$[\theta] \cdot 10^{-3}$	Comp.	Solv.[a]	λ_{max}	$[\theta] \cdot 10^{-3}$
1a	C	225	2.80	**1b**	C	225	2.46
	A	220	3.16		A	225	3.35
	M	219	4.22		M	220	3.58
1c	C	227	1.21				
	M	220	2.30				
2a	C	229	2.01	**2b**	C	225	4.48
	M	218	4.94		M	220	6.76
				2c	C	226	5.47
					M	218	8.47
3a	C	227	2.73	**3b**	C	226	2.28
	M	217	5.49		M	219	4.24
4a	C	225	9.0	**4b**	C	224	26.6
		261[b]	0.30			260[b]	0.42
	M	224	10.8		M	223	17.2
		261[b,c]	0.07			260[b]	0.13
5a	C	226	−4.69	**5b**	C	218	−3.88
		263[b]	−0.15			233	0.61
						261[b]	−0.24
					M	217	negative
						228	1.54
						262[b]	−0.22
6[d]	H	225	2.3				
	A	220	3.7				
	M	217.5	5.6				
7a[e]	M	215	−6.4	**7b**[e]	M	223	−2.4

[a]C—cyclohexane, A—acetonitrile, M—methanol, H—hexane; [b] the highest intensity vibronic band; [c]bisignate curve; [d]N. J. Greenfield and G. D. Fasman, *J. Am. Chem. Soc.* **92**, 177 (1970); [e]T. Wakabayashi, Y. Kato, K. Watanabe and M. Saito, *Chemistry Lett.* 461 (1977).



(a) (b)

Fig. 3. Folded (a) and unfolded (b) forms of (5S)-5-benzyl-4-oxazolidinone (**5**).

It is noteworthy that interactions between the rings in **5a** are more effective in conformation A' (enantiomeric to A) with axial benzyl, than in B with benzyl in bisectional position. However, distinction between these possibilities is difficult, since both forms give negative CD for $n \rightarrow \pi^*$ transition. Bisignate CD for **5b** after all shows predominance of folded conformation, and because form B diminishes interaction between C-2 methyl and phenyl groups in **5b**, this form seems to be more probable. The nature of interaction between the phenyl and oxazolidinone ring is not completely clear. In case of diketopiperazines Kopple suggested that permanent dipole of dipeptide moiety interacts with induced dipole in phenyl ring.[17] Although 4-oxazolidinones and 1,3-dioxolan-4-ones show similar values of dipole moment,[19] neither CD nor NMR spectra show the presence of folded form of 5-benzyl-1,3-dioxolan-4-one in solution.[7]

Since 4-oxazolidinones are heterocyclic analogues of γ-lactams it may be valuable to compare the chiroptical properties of these compounds. The most simple model of chiral γ-lactam is (+)-3-methylpyrrolidinone (**6**). This compound has positive $n \rightarrow \pi^*$ CD which magnitude becomes greater with increase of solvent polarity (Table 1),[20] analogous with **1a** and **2a**, and the predominance of envelope conformation with pseudoequetorial methyl in polar solvents is likewise expected.

Some controversies exist in assignment of absolute configuration for **6**.[20–23] Comparison of CD spectra for **6**, **1a** and **1b**, compounds which are close analogues, should be helpful. The mutual similarity of these spectra confirms that the configuration of **6** was correctly assigned to be R.[23] It is noteworthy that the Schellman quadrant rule predicts opposite CE signs for all these compounds. The spectra of **7a** and **7b** illustrate the influence of N-substituents on γ-lactam conformation. These data show that N-methylation of **7a** causes considerable diminution of CD. It can be rationalized by flattening of envelope conformation and/or decrease of its contribution to equilibrium in favor of enantiomeric puckered A' form with axial C-5 methyl group. This example is related to 2,3-vicinal interactions of 4-oxazolidinones mentioned above.

In conclusion, it may be stated that 1,3-dioxolan-4-ones and 4-oxazolidinones are simple and well-suited models for both experimental and theoretical investigations. Conformation of these compounds can be in principle established by classic conformational analysis basing on substituents interaction and then may serve as a basis for testing the sector rules governing CE sign for lactones and lactams.

EXPERIMENTAL

Spectroscopic measurements and CNDO calculations were carried out as described previously.[7] 4-Oxazolidinones were obtained from corresponding amides or N-methylamides of (S)-α-hydroxy acids and carbonyl compounds (paraformaldehyde was used as a source of CH_2O) by refluxing an equimolar mixture for 6 hr in benzene solution with catalytic amount of toluene-p-sulphonic acid. Water was trapped with a Dean-Stark apparatus. The reaction mixture after cooling was washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4) and benzene was evaporated at reduced pressure. The residue was distilled or crystallized from appropriate solvent.

(5S)-3,5-Dimethyl-4-oxazolidinone (**1a**). B.p. 98–100°/25 Torr; $[\alpha]_D^{20} = +34.4°$ (neat); NMR (δ, CCl_4): 4.80 (m, 2H), 4.0 (q, 1H), 2.74 (s, 3H); Found: N, 8.15; $C_9H_{17}NO_2$ requires N, 8.18%.

(5S)-2,2,5-*Trimethyl*-4-*oxazolidinone* (**1b**). Obtained according to the Fischer method,[24] m.p. 119°; $[\alpha]_D^{20} = +27.8°$ (c2.5, CCl_4); NMR: (δ, CCl_4): 9.37 (br, 1H), 4.18 (q, 1H), 1.37 (s, 3H) and 1.32 (s, 2H); Found: C, 56.01; H, 8.54; N, 10.72; $C_6H_{11}NO_2$ requires: C, 55.80; H, 8.58; N, 10.72.

(5S)-2,2-*Diethyl*-5-*methyl*-4-*oxazolidinone* (**1c**). Ootained analogously to the Fischer method m.p. 44–45°; $[\alpha]_D^{20} = +22°$ (c2, CCl_4); Found: C, 61.30; H, 9.63; N, 8.82; $C_8H_{15}NO_2$ requires: C, 61.12; H, 9.62; N, 8.91%.

(5S)-*Isopropyl*-3-*methyl*-4-*oxazolidinone* (**2a**). B.p. 97–98°/12 Torr; $[\alpha]_D^{20} = -34.5$ (neat); NMR (δ, CCl_4): 4.84 (m, 2H), 3.85 (m, 1H); 2.73 (s, 3H); Found: N, 9.80; $C_7H_{13}NO_2$ requires: N, 9.78%.

(5S)-5-*Isopropyl*-2,2-*dimethyl*-4-*oxazolidinone* (**2b**). M.p. 94–95°; $[\alpha]_D^{20} = -12.5°$ (c1, CCl_4); NMR (δ, CCl_4): 9.38 (br, 1H), 3.97 (d, 1H), 2.83(s, 6H); Found: C, 61.39; H, 9.37; N, 9.14; $C_8H_{15}NO_2$ requires: C, 61.12; H, 9.62; N, 8.91%.

(5S)-5-*Isopropyl*-2,2,3-*trimethyl*-4-*oxazolidinone* (**2c**). B.p. 110–112°/12 Torr; $[\alpha]_D^{20} = -16.6°$ (neat); NMR (δ, CCl_4): 3.89 (d, 1H); 2.67 (s, 3H); 1.33 (s, 3H) and 1.29 (s, 3H); Found: N, 8.25, $C_9H_{17}NO_2$ requires: N, 8.18%.

(5S)-5-*Isobutyl*-3-*methyl*-4-*oxazolidinone* (**3a**). B.p. 109–112°/12 Torr; $[\alpha]_D^{20} = -18.4°$ (neat); NMR (δ, CCl_4): 4.80 (m, 2H); 3.95 (m, 1H), 2.69 (s, 3H); Found: N, 8.97; $C_8H_{15}NO_2$ requires: N, 8.91%.

(5S)-5-*Isobutyl*-2,2-*dimethyl*-4-*oxazolidinone* (**3b**). M.p. 86–87°; $[\alpha]_D^{20} = -12°$ (c1, CCl_4); NMR (δ, CCl_4): 9.38 (br, 1H), 4.13 (m, 1H), 1.32 (s, 3H) and 1.30 (s, 3H); Found: C, 63.40; N, 8.14; H, 9.86; $C_9H_{17}NO_2$ requires: C, 63.13; N, 8.18: H, 10.0%.

(5S)-5-*Phenyl*-3-*methyl*-4-*oxazolidinone* (**4a**). M.p. 69–70°; $[\alpha]_D^{20} = -7°$ (c2, CCl_4); NMR (δ, CCl_4): 7.17 (m, 5H), 4.85 (m, 2H), 4.81 (m, 1H), 2.57 (s, 3H); Found: C, 67.85; N, 7.91; H, 6.12; $C_{10}H_{11}NO_2$ requires: C, 67.78; N, 7.90; H, 62.6%.

(5S)-5-*Phenyl*-2,2-*dimethyl*-4-*oxazolidinone* (**4b**). M.p. 122–124° $[\alpha]_D^{20} = +86°$ (c1, CCl_4); NMR (δ, CCl_4): 9.02 (br, 1H), 7.24 (m, 5H), 5.13 (s, 1H), 1.35 (s, 3H) and 1.32 (s, 3H); Found: C, 69.29; N, 7.58; H, 6.95; $C_{11}H_{13}NO_2$ requires: C, 69.09; N, 7.32; H, 6.85%.

(5S)-5-*Benzyl*-3-*methyl*-4-*oxazolidinone* (**5a**). M.p. 35–36°; $[\alpha]_D^{20} = -138°$ (c1.5, CCl_4); NMR (δ, CCl_4): 7.05 (s, 5H), 4.65 (m, 1H) and 4.30 (m, 1H), 4.25 (m, 1H), 2.87 (m, 2H), 2.50 (s, 3H); Found: C, 69.97; N, 6.63; H, 7.35; $C_{12}H_{15}NO_2$ requires: C, 70.22; N, 6.82; H, 7.37%.

(5S)-5-*Benzyl*-2,2-*dimethyl*-4-*oxazolidinone* (**5b**). M.p. 66–67°; $[\alpha]_D^{20} = -92°$ (C1.5, CCl_4); NMR (δ, CCl_4): 8.73 (br, 1H), 7.13 (s, 5H), 4.33 (m, 1H), 2.9 (m, 2H); 1.30 (s, 3H) and 1.08 (s, 3H); (Found: C, 69.97; N, 6.63; H, 7.35; $C_{12}H_{15}NO_2$ requires: C, 70.22; N, 6.82; H, 7.37).

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REFERENCES

[1]E. C. Ong, L. C. Cusachs, and O. E. Weigang, *J. Chem. Phys.* **67**, 3289 (1977).
[2]O. E. Weigang, *Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism* (Edited by F. Ciardelli and P. Salvadori). Chap. 2.3. Heyden, London (1973).
[3]W. Klyne and P. M. Scopes, Chap. 3.3 of ref 2.
[4]H. Basch, M. B. Robin and N. A. Kuebler, *J. Chem. Phys.* **49**, 5007 (1968).
[5]W. Klyne, D. N. Kirk, J. Tilley and H. Suginome, *Tetrahedron* **36**, 543 (1980).
[6]T. Konno, H. Meguro and K. Tutzimura, *Tetrahedron Letters* 1305 (1975).
[7]T. Połoński, *Tetrahedron* **39**, 3131 (1983).
[8]J. W. Cornforth, *Heterocyclic Compounds* (Edited by R. C. Elderfield), Vol. 5, pp. 298 and 402. Wiley, New York (1957).
[9]J. B. Bicking, S. F. Kwong, M. H. Fischer and W. H. Nicholson, *J. Med. Chem.* **8**, 95 (1965).
[10]J. A. Molin-Case, E. Fleischer and D. W. Urry, *J. Am. Chem. Soc.* **92**, 4728 (1970).
[11]H. Wolf, *Tetrahedron Letters* 1075 (1965); A. F. Beecham, *Ibid.* 3591 (1968) and 4897 (1969); H. Ogura, H. Takayanagi and K. Furuhata, *Chem. Letters* 387 (1973).

[12]H. Ogura, H. Takayanagi, K. Kubo and K. Furuhata, *J. Am. Chem. Soc.* **95**, 8056 (1973).
[13]B. J. Litman and J. A. Schellman, *J. Phys. Chem.* **69**, 978 (1965); J. A. Schellman, *Acc. Chem. Res.* **1**, 144 (1968).
[14]T. Wakabayashi, Y. Kato, K. Watanabe and M. Saito, *Chem. Letters* 461 (1977).
[15]P. Maloň, S. Bystrický and K. Bláha, *Coll. Czechoslov. Chem. Commun.*, **43**, 781 (1978) and refs therein.
[16]CNDO/2 calculations show total energy equal −2003.3074 eV for planar B form and −2003.3059 eV for the same form with N–H bond distorted by 10° from the ring plane.
[17]K. D. Kopple and D. H. Marr, *J. Am. Chem. Soc.* **89**, 6193 (1967); K. D. Kopple and M. Ohnishi, *Ibid.* **91**, 962 (1969).
[18]G. Gawne, G. W. Kenner, N. H. Rogers, R. C. Sheppard and K. Titlestad, *Peptides* 1968, p. 28. North Holland, Amsterdam (1968); K. Blaha and I. Frič, *Coll. Czechoslov. Chem. Commun.* **35**, 619 (1970); L. E. Webb and C. F. Lin, *J. Am. Chem. Soc.* **93**, 3818 (1971); J. W. Snow and T. M. Hooker, Jr., *Ibid.* **97**, 3506 (1975); R. Deslauriers, Z. Grzonka, K. Schaumburg, T. Shiba and R. Walter, *Ibid.* **97**, 5093 (1975).
[19]CNDO/2 calculations show dipole moments equal 2.20 and 2.72 D for unsubstituted planar 1,3-dioxolan-4-one and 4-oxazolidinone respectively.
[20]N. J. Greenfield and G. D. Fasman, *J. Am. Chem. Soc.* **92**, 177 (1970).
[21]D. Fleš and T. Ghyczy, *Croatl. Chem. Acta* **36**, 27 (1964); R. Adams and D. Fleš, *J. Am. Chem. Soc.* **81**, 4946 (1959).
[22]R. E. Geiger and G. H. Wagniére, *Helv. Chim. Acta* **58**, 738 (1975); F. S. Richardson, R. Strickland and D. D. Shillady, *J. Phys. Chem.* **77**, 248 (1973); A. P. Volosov, V. A. Zubkov and T. M. Birshtein, *Tetrahedron* **32**, 1259 (1975).
[23]B. Ringdahl and R. Dahlbom, *Tetrahedron Letters* **37**, 3475 (1978).
[24]H. O. L. Fischer, G. Dangschat and H. Stettiner, *Chem. Ber.* **65**, 1032 (1932).