Reaction of 1,1'-Iminobis-2-butanols with Sulfuric Acid

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Treatment of 1,1'-iminobis-2-butanols with 70% w/w sulfuric acid gives *cis*- and *trans*-2,6-diethylmorpholines, 3-ethyl-4-methylpyridine and unsaturated 3-ethyl-4-methylpiperidines. Hydrogenation of the unsaturated 3-ethyl-4-methylpiperidines gives *cis*- and *trans*-3-ethyl-4-methylpiperidines. With 50% w/w sulfuric acid *cis*- and *trans*-2,6-diethylmorpholines and a small amount of *cis*- and *trans*-2-ethyl-7-methyl-hexahydro-1,4-oxazepines are obtained.

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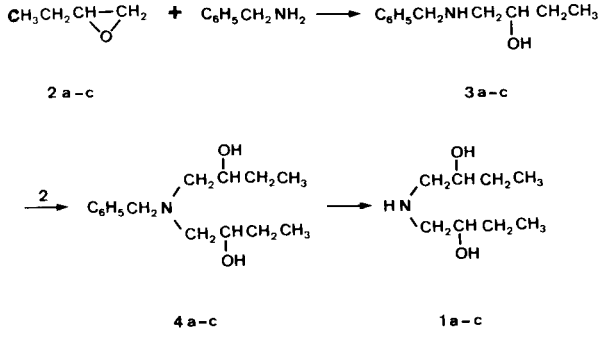
In previous papers [1,2] from our laboratory we have shown that the reaction between tri- and tetramethyl substituted diethanolamines and 70% w/w sulfuric acid gives morpholines with good to excellent yields. During the course of further studies [3,4,5,6] to elucidate the reaction mechanism we observed that the ring closure seems to follow exclusively an S_N2-type mechanism with partial inversion of configuration before the cyclization. However, the exact mechanism of this inversion still remains a subject for conjecture.

In continuation of our previous work we have now studied the ring closure of the 1,1'-iminobis-2-butanols.

The 1,1'-iminobis-2-butanols (**1a-c**) are prepared from (*S*)-(-)-1,2-epoxybutane [7], (*R*)-(+)-1,2-epoxybutane [8] and commercial DL-1,2-epoxybutane (**2a-c**) following the synthetic route outlined in Scheme I and using standard conditions.

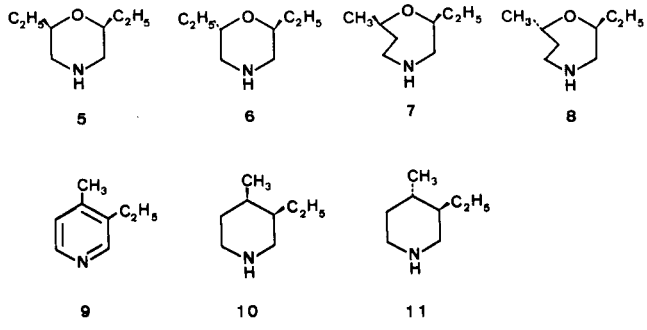
Scheme I



The 1-benzylamino-2-butanols (**3a-c**) have to be purified from about 4% 2-benzylamino-1-butanol by recrystallization. Otherwise 2,5-diethylmorpholines will be formed in the ring closure reactions.

The 1,1'-iminobis-2-butanols (**1a-c**) are treated with a large excess of sulfuric acid at 145° [1]. The reaction mixture is made alkaline and extracted with diethyl ether. The resulting reaction product is distilled and hydrogenated in dioxane with 10% palladium on charcoal as catalyst at 80° and 1500 psi. The products obtained are shown in Scheme II and the results of the ring closure are summarized in Table 1.

Scheme II



The assignments of the compounds **5** and **6** are routine and therefore are discussed only in Experimental. The nmr spectra of the compounds **7** and **8** are shown in Figure 1. Inspection of the 7-CH-groups (a and b) gives an unambiguous assignment of the *cis* and *trans* isomers (see Experimental). The nmr spectra of **10** and **11** are complex. Decoupling of the 4-CH_3-group of compound **10** gives a methine group composed of a doublet of two triplets (δ = 1.88; J = 4.5; J = 4.5) which means that this compound tentatively can be assigned *cis*.

Treatment of (*S*:*S*)-1,1'-iminobis-2-butanol with 70% w/w sulfuric acid at 145° gives 38% *cis*-2,6-diethylmorpholine presumably formed mainly by an S_N2-mechanism. Only 4% of the *trans* isomer is obtained which means that the inversion (or any other mechanism) after which the *trans* isomer is formed is of minor importance. The glc of the reaction product shows that besides the two morpholines at least three unsaturated piperidines and 1% 3-ethyl-4-methylpyridine [9] are formed. While unsaturated piperidines are unstable under the conditions used in preparative glc, hydrogenation of the reaction product transforms all unsaturated compounds into *cis*- and *trans*-3-ethyl-4-methylpiperidines [10]. The unsaturated piperidines might be formed by elimination of two molecules of water from 1,1'-iminobis-2-butanol giving dicrotylamine followed by intramolecular cyclization. A similar cyclization of

Table 1

1,1'-Iminobis-2-butanol	Sulfuric acid (% w/w)	Reaction time hours	Reaction products % 5	6	7	8	9	10	11
S:S (**1a**)	50	24	47	4	2	2			
	70	15	38	4			1	2	6
S:R (**1b**)	50	24	20	18	3	2			
	70	15	22	13			2	5	15
DL + meso (**1c**)	50	24	35	10	2	2			
	70	15	25	8			3	5	14

di-γ-chlorocrotylamines to 3-acetyl-4-methyl-1,2,5,6-tetrahydropyridines by sulfuric acid has been described by R. Lukeš *et al.* [11]. The formation of pyridine might mean that oxidation and/or disproportionation reactions occur as expected in the reaction mixture.

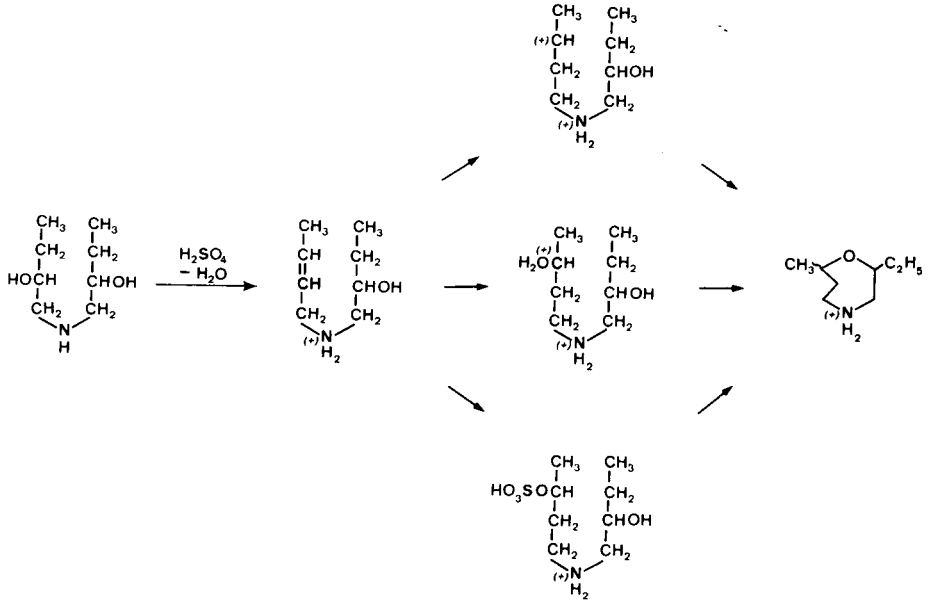
If 50% w/w sulfuric acid is used instead only traces of unsaturated piperidines are obtained and the ratio *cis*/*trans* of the 2,6-diethylmorpholines increases slightly. Glc gives evidence of two new compounds which are isolated and shown to be *cis*- and *trans*-2-ethyl-7-methylhexahydro-1,4-oxazepines. Conceivably, there are a number of ways in which they can be formed (*e.g.* see Scheme III).

Which of these routes is the most probable remains undetermined for the time being.

Whether the hexahydro-1,4-oxazepines are formed when using 70% w/w sulfuric acid has not been established. Both *cis*- and *trans*-2-ethyl-7-methyl-hexahydro-1,4-oxazepines are decomposed in 70% w/w sulfuric acid at 145° giving 45-80% of unsaturated piperidines which upon hydrogenation give *cis*- and *trans*-3-ethyl-4-methylpiperidines. The formation of the hexahydro-1,4-oxazepines is surprising. M. Lj. Mihailović *et al.* [12] have shown that treatment of ω-alkenols containing more remote double bounds such as 5-hexen-1-ol with sulfuric acid (25% v/v) at steam bath temperature results in the formation of 2-methyltetrahydropyran and 2-ethyltetrahydrofuran, 6-hepten-1-ol gives 2-ethyltetrahydropyran and 2-propyltetrahydrofuran, as well as the nonformation of seven-membered cyclic ethers in both cases.

Treatment of (S:R)-1,1'-iminobis-2-butanol with 70% w/w sulfuric acid gives 22% *cis*-2,6-diethylmorpholine and 13% of the *trans* isomer. This means that only to a small degree the reaction follows an S_N2-pattern, while the main route(s) give(s) the more sterically hindered *cis* isomer. Apart from the inversion of the diol and an S_N2 cyclization it cannot be excluded that the monocrotylamine derivative in one way or the other is an intermediate in the formation of the 2,6-diethylmorpholines. The same type of mechanism as in the formation of the hexahydro-1,4-oxazepines might be assumed (see Scheme III). The yield of piperidines using the (*S:R*)-isomer is substantially higher, which

Scheme III



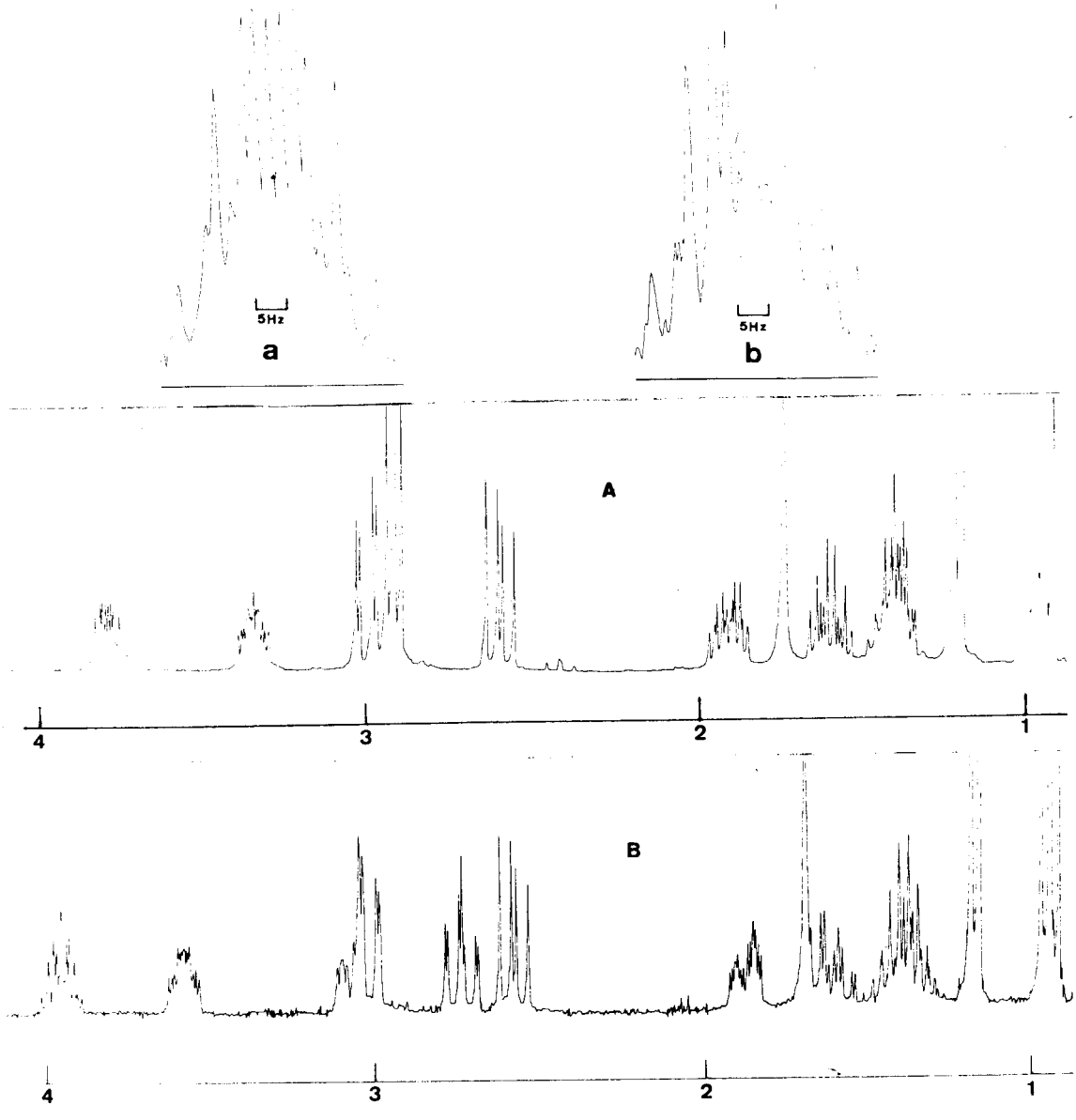


Figure 1. The 270 MHz ^{1}H-nmr spectra of the 2-ethyl-7-methylhexahydro-1,4-oxazepines. A is assigned *trans* and B *cis*. a and b are enlargements of the 7-CH-groups of the two isomers.

means that more dicrotylamine is formed during the reaction. From a synthetic standpoint this type of cyclization of 1,1'-iminobis-2-alkanols might provide a potentially useful route to 3,4-dialkylpiperidines. The inexpensiveness and ready availability of starting materials add to the attractiveness of this method. Use of 50% w/w sulfuric acid increases the ration *trans*/*cis* of the 2,6-diethylmorpholines which means that the S_N2 ring closure occurs to a greater extent under mild conditions. The amount of *cis*- and *trans*-2-ethyl-7-methylhexahydro-1,4-oxazepines formed during the reaction is about the same as for the (*S*:*S*)-isomer.

A. Ya. Berlin *et al.* [13] cyclized 1,1'-iminobis-2-butanols (1 mole) in the presence of concentrated sulfuric acid (1.5 moles) at 170-180° for 8 hours and obtained a yield of 70% of 2,6-diethylmorpholine. However, their paper contains no discussion about or demonstration of *cis* and *trans* isomers.

EXPERIMENTAL

GLC.

The analyses were performed on a Varian 3700 instrument. The separ-

ation of the various compounds was carried out as described earlier [1,2]. As *cis*-2,6-diethylmorpholine and *trans*-2-ethyl-7-methylhexahydro-1,4-oxazepine only gave one peak on our preparative columns they were separated as *N*-benzyl derivatives using a rather short column (4.5 m × 6.7 mm with 20% Carbowax 20 M + 3% (potassium hydroxide on Chromosorb A 60/80), temperature 170-190° and a nitrogen flow of about 50 ml/minute. The resolution was not good enough to produce pure fractions in one run. A second run of the separated crude fractions gave compounds of about 98% purity.

Preparation of (*S*)-1-Benzylamino-2-butanol (**3a**).

(*S*)-(-)-1,2-Epoxybutane (710 mg 0.01 mole) [7], 5.4 g (0.05 mole) of benzylamine and 50 ml of 96% ethanol were heated together in a stainless steel autoclave at 150° for 2 hours. The reaction product was distilled to give 1.50 g (84%) of (*S*)-1-benzylamino-2-butanol, bp 145-147° (8 mm), mp 43-44° from methylcyclohexane.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81; O, 8.93. Found: C, 73.6; H, 9.80; N, 7.78; O, 8.85.

Prepration of (*R*)-1-Benzylamino-2-butanol (**3b**).

This compound was prepared as above from (*R*)-(+)-1,2-epoxybutane [8] giving crystals of (*R*)-1-benzylamino-2-butanol, mp 43-44° from methylcyclohexane.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81; O, 8.93. Found: C, 73.3; H, 9.76; N, 7.72; O, 9.00.

Preparation of DL-1-Benzylamino-2-butanol (**3c**).

This compound was prepared as above from commercial 1,2-epoxybutane giving crystals of DL-1-benzylamino-2-butanol, mp 45-46° from methylcyclohexane. No mp is reported by I. Okada *et al.* [14].

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81; O, 8.93. Found: C, 73.6; H, 9.80; N, 7.78; O, 8.85.

Preparation of (*S*:*S*)-*N*-Benzyl-1,1'-iminobis-2-butanol (**4a**).

(*S*)-1-Benzylamino-2-butanol (**3a**) (1.79 g 0.01), 800 mg (0.011 mole) of (*S*)-(-)-1,2-epoxybutane and 25 ml of 96% ethanol were heated together in a stainless steel autoclave at 150° for 5 hours. The reaction product was distilled to give 2.40 g (96%) of (*S*:*S*)-*N*-benzyl-1,1'-iminobis-2-butanol, bp 122-125°/0.05 mm. The hydrochloride, recrystallized from ethanol diethyl ether, had mp 168-169°.

Anal. Calcd. for $C_{15}H_{26}ClNO_2$: Cl, 12.32. Found: Cl, 12.2

Preparation of (*S*:*R*)-*N*-Benzyl-1,1'-iminobis-2-butanol (**4b**).

This compound was prepared as above from **3b** and (*S*)-(-)-1,2-epoxybutane. The hydrochloride, recrystallized from ethyl acetate, had mp 93-96°.

Anal. Calcd. for $C_{15}H_{26}ClNO_2$: Cl, 12.32. Found: Cl, 12.1.

Preparation of (*S*:*S*)-1,1'-Iminobis-2-butanol (**1a**).

(*S*:*S*)-*N*-Benzyl-1,1'-iminobis-2-butanol (**4a**) (2.51 g, 0.01 mole) was hydrogenated in 50 ml of dioxane over 0.1 g of palladium on charcoal at 80° and at 1500 psi in a stainless steel autoclave with efficient stirring. The filtrate obtained from the hydrogenation was evaporated. The residue (1.79 g, 100%) crystallized, mp 60-62° after recrystallization from ligroin (bp 80-110°).

Anal. Calcd. for $C_8H_{19}NO_2$: C, 59.59; H, 11.88; N, 8.69; O, 19.85. Found: C, 59.3; H, 12.0; N, 8.62; O, 19.7.

Preparation of (*S*:*R*)-1,1'-Iminobis-2-butanol (**1b**).

This compound was prepared as above from (**4b**), crystals, mp 56-57° from ligroin (bp 80-110°).

Anal. Calcd. for $C_8H_{19}NO_2$: C, 59.59; H, 11.88; N, 8.69; O, 19.85. Found: C, 59.3; H, 12.1; N, 8.59; O, 19.6.

cis-2,6-Diethylmorpholine (**5**).

This compound had the following physical data: ^{1}H-nmr (deuteriochloroform: TMS): δ 0.94 (t, 6H, CH_3), 1.45 (m, 4H, CH_2), 2.37-2.88 (qq, 4H, CH_2; J = 12.28, J = 10.40, J = 2.10); 3.30 (m, 2H, CH). Compare *cis*-2,6-dimethylmorpholine [15].

N-Phenyl-*cis*-2,6-diethylmorpholine-4-thiocarboxamide.

This compound had mp 106-108° [13].

Anal. Calcd. for $C_{15}H_{22}N_2OS$: N, 10.06; S, 11.52. Found: N, 10.2; S, 11.5.

(*S*)-*N*-(1-Phenylethyl)-*cis*-2,6-diethylmorpholine-4-carboxamide.

This compound had mp 109-111°.

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.57; H, 9.02; N, 9.65. Found: C, 70.7; H, 9.07; N, 9.59.

trans-2,6-Diethylmorpholine (**6**).

This compound had the following physical data: ^{1}H-nmr (deuteriochloroform: TMS): δ 0.93 (t, 6H, CH_3), 1.44 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 2.55-2.94 (qq, 4H, CH_2; J = 12.12, J = 5.72, J = 3.40), 3.55 (m, 2H, CH). Compare *trans*-2,6-dimethylmorpholine [15].

N-Phenyl-*trans*-2,6-diethylmorpholine-4-thiocarboxamide.

This compound had mp 120-122°.

Anal. Calcd. for $C_{15}H_{22}N_2OS$: N, 10.06; S, 11.52. Found: N, 10.1; S, 11.8.

cis-2-Ethyl-7-methylhexahydro-1,4-oxazepine (**7**).

This compound had the following physical data: n^{24}_D = 1.4543; ^{1}H-nmr: (see Fig. 1) δ 3.94 (m, H, CH; J = 10.5, J = 6.4, J = 4.2).

N-Benzyl-*cis*-2-ethyl-7-methylhexahydro-1,4-oxazepine Hydrochloride.

This compound had mp 137-139°.

Anal. Calcd. for $C_{15}H_{24}ClNO$: Cl, 13.14. Found: Cl, 13.2.

trans-2-Ethyl-7-methylhexahydro-1,4-oxazepine (**8**).

This compound had the following physical data: n^{24}_D = 1.4508; ^{1}H-nmr: (see Fig. 1) δ 3.78 (m, H, CH; J = 6.3, J = 4.6, J = 3.0).

N-Phenyl-*trans*-2-ethyl-7-methylhexahydro-1,4-oxazepine-4-thiocarboxamide.

This compound had mp 89-91°.

Anal. Calcd. for $C_{15}H_{22}N_2OS$: N, 10.06; S, 11.52. Found: N, 10.2; S, 11.7.

N-Phenyl-*cis*-3-ethyl-4-methylpiperidine-1-thiocarboxamide.

This compound had mp 108-110°.

Anal. Calcd. for $C_{15}H_{22}N_2S$: N, 10.68; S, 12.22. Found: N, 10.7; S, 12.1.

N-Phenyl-*trans*-3-ethyl-4-methylpiperidine-1-thiocarboxamide.

This compound had mp 97-99°.

Anal. Calcd. for $C_{15}H_{22}N_2S$: N, 10.68; S, 12.22. Found: N, 10.8; S, 12.5.

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REFERENCES AND NOTES

[1] S. Hernestam and G. Stenvall, *J. Heterocyclic Chem.*, **13**, 733 (1976).

[2] S. Hernestam, B. Nilsson and G. Stenvall, *ibid.*, **14**, 899 (1977).

[3] S. Hernestam, *ibid.*, **16**, 595 (1979).

[4] S. Hernestam, *ibid.*, **16**, 1253 (1979).

[5] S. Hernestam and G. Stenvall, *ibid.*, **17**, 369 (1980).

[6] S. Hernestam and G. Stenvall, *ibid.*, **17**, 1751 (1980).

[7] B. Seuring and D. Seebach, *Helv. Chim. Acta*, **60**, 1175 (1977);

E. Hungerbühler, R. Naef, O. Wasmuth, D. Seebach, H.-R. Loosli and A. Wehrli, *ibid.*, **63**, 1960 (1980).

[8] J. L. Coke and R. S. Shue, *J. Org. Chem.*, **38**, 2210 (1973).

[9] D. L. Boger and J. S. Panek, *ibid.*, **46**, 2179 (1981); ref [8] therein.

[10] W. Koenigs and K. Bernhart, *Ber.*, **38**, 3042 (1905); M. de Montmollin and M. Martenet, *Helv. Chim. Acta*, **12**, 604 (1929).

[11] R. Lukeš, M. Hudlický and Z. Janu, *Collect. Czech. Chem. Commun.*, **21**, 140 (1956), and references cited therein.

[12] M. Lj. Mihailović, N. Orbović, D. Marinković and S. Konstantinović, *Bull. Soc. Chim. Beograd*, **44**, 597 (1979).

[13] A. Ya. Berlin and T. P. Sycheva, *J. Gen. Chem. USSR*, **20**, 677 (1950).

[14] I. Okada, K. Ichimura and R. Sato, *Bull. Chem. Soc. Japan*, **43**, 1185 (1970).

[15] H. Booth and G. C. Gidley, *Tetrahedron*, **21**, 3429 (1965).