Reaction of *N*-Benzyl-1,1'-iminobis-2-butanols with 70% w/w Sulfuric Acid

Sven Hernestam [1] and Gillis Stenvall

Department of Organic Chemistry, Research Division, AB Ferrosan,
Box 839, S-201 80 Malmö, Sweden

Thomas Olsson

Department of Organic Chemistry, Chalmers University of Technology,
S-412 96 Göteborg, Sweden
Received September 28, 1983

Treatment of *(S:R)*-*N*-benzyl-1,1'-iminobis-2-butanol with 70% w/w sulfuric acid gives *cis*- and *trans*-*N*-benzyl-2,6-diethylmorpholines (15 and 74%, respectively) and *N*-alkenyl-4-ethyl-1,2,3,4-tetrahydroisoquinolines (5%). Hydrogenation of the reaction mixture gives *cis*- and *trans*-2,6-diethylmorpholines and *N*-butyl-4-ethyl-1,2,3,4-tetrahydroisoquinoline. Neither *N*-benzyl-*N*-crotyl-(2-hydroxy-1-butyl)amine (4) nor *N*-benzyldicrotylamine (5) are intermediates in the reaction. *(S:S)*-*N*-Benzyl-1,1'-iminobis-2-butanol gives 95% of *cis*-*N*-benzyl-2,6-diethylmorpholine and 1% of the *trans* isomer.

In our previous paper [2] we reported that treatment of 1,1'-iminobis-2-butanols with 70% w/w sulfuric acid gives *cis*- and *trans*-2,6-diethylmorpholines, unsaturated 3-ethyl-4-methylpiperidines, and 3-ethyl-4-methylpyridine. We have suggested that the formation of morpholines seems to exclusively follow an S_N2-like ring closure mechanism [3,4,5,6] with partial inversion of configuration before the cyclization. However, it cannot be excluded that there is an alternate route over a monocrotylamine (4) to the 2,6-diethylmorpholines [2]. In continuation of our previous work we have now studied the ring closure of the *N*-benzyl-1,1'-iminobis-2-butanols [2] with 70% w/w sulfuric acid.

The *N*-benzyl-1,1'-iminobis-2-butanols are treated with a large excess of 70% w/w sulfuric acid at 145° for 15 hours [7]. The reaction mixture is made alkaline and extracted with diethyl ether. The reaction product is distilled and hydrogenated in acetic acid with 10% palladium on charcoal as catalyst at room temperature and 50 psi for 72 hours. The products obtained are shown in Figure 1 and the results of the ring closure are summarized in Table 1.

Treatment of *(S:R)*-*N*-benzyl-1,1'-iminobis-2-butanol [2] gives 74% of *trans*-2,6-diethylmorpholine (2). Fifteen per cent of the *cis* isomer (1) is obtained, which means that inversion (or any other mechanism) according to which the *cis* isomer was formed occurs to a substantial degree. Beside the two morpholines 5% of *N*-butyl-4-ethyl-1,2,3,4-tetrahydroisoquinoline (3) was isolated. To try to elucidate

the mechanism by which the isoquinoline was formed *N*-benzyl-*N*-crotyl-(2-hydroxy-1-butyl)amine (4) and *N*-benzyl-dicrotylamine (5) were cyclized in the standard way. The reaction of 4 and 5 gave a host of compounds of which only a few have been isolated (see Scheme 1 and Table 2).

These results suggest that neither *N*-benzyl-*N*-crotyl-(2-hydroxy-1-butyl)amine (4) nor *N*-benzyldicrotylamine (5) are intermediates in the ring closure of *(S:R)*-*N*-benzyl-1,1'-iminobis-2-butanols (see Table 1) as no traces of 3-ethyl-4-methylpiperidines (11 and 12) and *N*-butyl-5-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (9) or 3-(2-methylphenyl)dibutylamine (10) have been detected in the hydrogenated reaction mixture. This also means that formation of the *N*-benzyl-2,6-diethylmorpholines *via* a crotyl intermediate (4) can be excluded.

When the reduction was run for 72 hours most of the 2,3,4,5-tetrahydro-1*H*-2-benzazepine ring system undergoes cleavage and 3-(2-methylphenyl)dibutylamine (10) was formed. It was isolated as the hydrochloride (see Experimental). Under these conditions the 1,2,3,4-tetrahydroisoquinoline ring is stable [8]. However, when the reaction mixture from the ring closure of *N*-benzyl-1,1'-iminobis-2-butanol was hydrogenated in dioxane with 10% palladium on charcoal at 120° and 2000 psi some of 3 was transformed into 2-(2-methylphenyl)dibutylamine (13) (see Experimental).
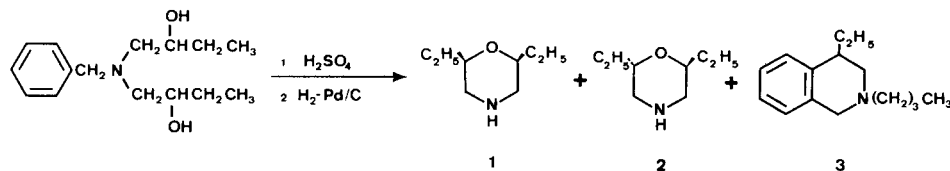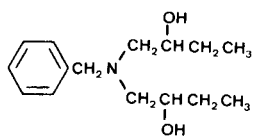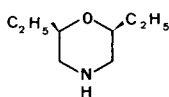

FIG 1
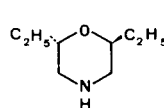
Table 1
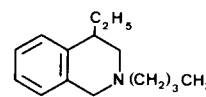
N-Benzyl-1,1'-iminobis-2-butanol		Reaction Products %	
	1	2	3
S:R	15	74	5
S:S	95	1	trace
DL + meso	54	38	3

Table 2

Amine	Reaction Products %					
	1	2	3	9 and/or 10	11	12
4	2	1	9	7	11	5
5	—	—	1	3	15	8
6	—	—	3	94	—	—
7	—	—	4	94	—	—
8	—	—	46	48	—	—

In addition to the two crotylamines **4** and **5** compounds **6, 7** and **8** were treated in the standard way; only the hydrogenation step was excluded. The results are summarized in Table 2. Compound **6** gave 94% of N-butyl-5-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine (**9**) and 3% of N-butyl-4-ethyl-1,2,3,4-tetrahydroisoquinoline (**3**). Venkataramu et al. [9] have shown that benzylammonium salts possessing a crotyl chain in the presence of 115% polyphosphoric acid at 300° for 1 hour furnish seven-membered 2,3,4,5-tetrahydro-1H-2-benzazepinium salts in considerable yields (55-67%). No 1,2,3,4-tetrahydroisoquinolinium salts were formed. They suggest that protonation of
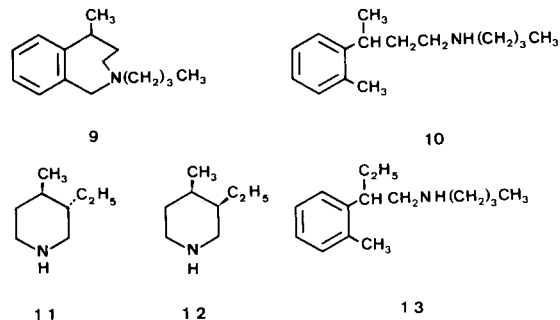
SCHEME I

the olefinic bond must have occurred to produce a cation at the γ carbon (in relation to N⁺) rather than a cation at the alternate β position. The results imply that 1) a cation intermediate is probably more stable at the γ position than a cation at the β position (hyperconjugative effect) or 2) protonation is favoured at the γ position in order to place the positive centers at the most remote positions creating a more stable intermediate owing to less charge repulsion followed by an electrophilic attack on the benzene ring. Compound **7** gave the same yields of the six- and seven-membered ring compounds as **6**.

This means either that a γ cation might be formed directly from the secondary hydroxyl group and/or that it might be formed from the intermediate olefinic compound **6**. Compound **8** on the other hand gives 46% of the 1,2,3,4-tetrahydroisoquinoline derivative **3** and 48% of the 2,3,4,5-1*H*-2-benzazepine derivative **9**. This means that a β cation most probably is formed directly from the hydroxyl group before the electrophilic attack on the benzene ring. The 2,3,4,5-tetrahydro-1*H*-2-benzazepine ring might be obtained from the intermediate alkene **6** that is formed by an E1 elimination from the β cation. Mendelson *et al.* [10] have presented a Friedel-Crafts synthesis of 1,2,3,4-tetrahydroisoquinolines bearing electron withdrawing groups starting from 2-benzylaminoethanols and using ammonium chloride and aluminium chloride as ring closure agents at 185°. Although the issue of direct formation of products remains unresolved the conversion of aminoalcohols to the corresponding amino halides appears to be an important step in the reaction. Sulfuric acid is also used as catalyst for this ring closure. No results or mechanisms using that acid are disclosed in that paper. Schwan *et al.* [11] have reported synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinolines by ring closure of 2-benzylamino-1-phenylethanols with refluxing hydrobromic acid and polyphosphoric acid. A carbonium ion resulting from the acid treatment of the benzylcarbinols can be invoked in the pathways leading to both the 1,2,3,4-tetrahydroisoquinolines and the cleavage products. Attempted cyclization of dephenyl compounds resulted only in the isolation of the starting material. Hoffman *et al.* [12] have used sulfuric acid for the same type of ring closure. The use of this method can especially be found in the patent literature. Furthermore, *e.g.* Bobowski *et al.* [13] have shown that concentrated sulfuric acid as well as 60% sulfuric acid are effective cyclizing agents for 2-benzylamino-1-phenylethanols and α-[1-{(2-arylethyl)amino}-1-methylethyl]arylmethanols giving 1,2,3,4-tetrahydroisoquinolines and 2,3,4,5-tetrahydro-1*H*-3-benzazepines, respectively. The results with the model compounds **4-8** indicate that no normal β cation may exist in the ring closure of *(S:R)-N*-benzyl-1,1'-iminobis-2-butanol. In an attempt to mechanistically account for our experimental findings we offer the tentative working hypo-

thesis that the electrophilic attack on the benzene ring takes place in the transition state of the S_N2 ring closure reaction in which both the two hydroxy groups and the amino group are supposed to be involved. The geometry of the S_N2 transition state is such that steric factors might well be important. Furthermore, we believe that an aziridine-like ring structure might exist in the transition state [6] without a real covalent bond between the nitrogen atom and the β carbon atom. The charge distribution in the ammonium-carbonium ion, stabilized by the β' hydroxy group is such that neither an S_N1-type ring closure to *cis*- and *trans*-*N*-benzyl-2,6-diethylmorpholines nor an E1 elimination to the crotyl derivative **4** takes place. On the other hand, we believe that the postulated three-membered ring structure can react either with a water molecule and/or a sulfuric acid molecule giving randomly both *S* and *R* configurations at the β and β' carbon atoms (inversion) or as an electrophilic center attacking the benzene ring. However, more precise mechanistic study with regard to this intricate ring closure remains to be done.

Treatment of *(S:S)-N*-benzyl-1,1'-iminobis-2-butanol [2] in the standard way gave 95% *cis*-2,6-diethylmorpholine formed by an S_N2 mechanism. One per cent of the *trans* isomer was obtained which means that inversion is of minor importance in this ring closure. Furthermore, only traces of *N*-butyl-4-ethyl-1,2,3,4-tetrahydroisoquinoline could be detected by glc. This means that the sterical and electronic arrangement in the S_N2 transition state are suitable for a ring closure giving the more sterically hindered *cis* isomer in practically quantitative yield.

EXPERIMENTAL

GLC.

The analyses were performed on a Varian 3700 instrument. The separation of the various compounds was carried out as described earlier [7,14]. The crotyl derivatives **4, 5** and **6** appear as mixtures of isomers. Unfortunately, we have not yet been able to separate these compounds into pure isomers on a preparative scale.

Ring Closure of (DL + *meso*)-*N*-Benzyl-1,1'-iminobis-2-butanol.

(DL + *meso*)-*N*-Benzyl-1,1'-iminobis-2-butanol (251 g, 1 mole) was added with stirring and cooling to 750 ml of 70% w/w sulfuric acid. The mixture was kept in a glass autoclave at 145° for 15 hours. An excess of 20% sodium hydroxide solution was added with stirring and efficient cooling. The organic layer was separated and the residue extracted with several portions of diethyl ether. The combined organic phases were dried over sodium sulfate, filtered and evaporated. Distillation gave a fraction of 221 g, bp 90-95° (0.1 mm).

Catalytic hydrogenation of 116,5 g of the reaction product in 250 ml of dioxane over 4 g of 10% palladium on charcoal was performed at 120° and at 2000 psi in a stainless steel autoclave with efficient stirring. After about 8 hours no more hydrogen was absorbed. To the filtrate obtained

from the hydrogenation, 75 ml of concentrated hydrochloric acid was added, whereupon the dioxane, and the water were evaporated under good vacuum. An excess of 20% sodium hydroxide solution was added to the residue with efficient cooling. The product was extracted with diethyl ether and the ether extract dried over sodium sulfate. The ether was evaporated. The residue was distilled to give 69.3 g of cis- and trans-2,6-diethylmorpholines, bp 176-179°, and 3.7 g, bp 90-95° (0.1 mm), of a colourless liquid which by glc proved to be two compounds (50:50). They were separated by preparative glc. The first fraction (1.74 g) was 2-(2-methylphenyl)dibutylamine (13); ^{1}H-nmr: δ 0.81 (t, 3H, CH₃), 0.85 (t, 3H, CH₃), 1.20-1.27 (m, 2H, CH₂), 1.29-1.43 (m, 2H, CH₂), 1.52-1.75 (mm, 2H, CH₂), 2.34 (s, 3H, CH₃), 2.48-2.56 (m, 2H, CH₂), 2.75-2.88 (m, 2H, CH₂), 3.04-3.10 (m, H, CH), 7.03-7.24 (m, 4H, C₆H₄).

The hydrochloride, recrystallized from ethanol-diethyl ether, had mp 115-118°.

Anal. Calcd. for $C_{15}H_{25}N \cdot HCl$: C, 70.42; H, 10.24; Cl, 13.86; N, 5.48. Found: C, 70.1; H, 10.4; Cl, 13.8; N, 5.22.

The second fraction was N-butyl-4-ethyl-1,2,3,4-tetrahydroisoquinoline (3); ^{1}H-nmr: δ 0.93 (t, 3H, CH₃), 0.97 (t, 3H, CH₃), 1.33-1.44 (m, 2H, CH₂), 1.50-1.61 (m, 2H, CH₂), 1.70-1.79 (m, 2H, CH₂), 2.40-2.50 (m, 2H, CH₂), 2.61 (d, 2H, CH₂), 2.70-2.75 (m, H, CH), 3.43-3.67 (q, 2H, CH₂), 6.95-7.16 (m, 4H, C₆H₄).

The hydrochloride, recrystallized from ethanol-diethyl ether, had mp 178-180°.

Anal. Calcd. for $C_{15}H_{23}N \cdot HCl$: C, 70.98; H, 9.53; Cl, 13.97; N, 5.52. Found: C, 70.8; H, 9.82; Cl, 13.9; N, 5.43.

Catalytic hydrogenation of 58.25 g of the reaction product in 150 ml of glacial acetic acid over 5 g of 10% palladium on charcoal was performed at room temperature at 50 psi in a glass bottle with efficient shaking. After about 72 hours no more hydrogen was absorbed. The isolation of the reaction products was carried out as above. Thirty-four g of cis- and trans-2,6-diethylmorpholines and 1.77 g of N-butyl-4-ethyl-1,2,3,4-tetrahydroisoquinoline (3) were obtained.

N-Butyl-5-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine (9).

This compound has the following physical data: ^{1}H-nmr: δ 0.89 (t, 3H, CH₃), 1.24-1.34 (m, 2H, CH₂), 1.36 (d, 3H, CH₃), 1.42-1.50 (m, 2H, CH₂), 1.62-1.68 (m, 2H, CH₂), 2.29-2.36 (m, 2H, CH₂), 2.93-3.02 (m, H, CH), 3.08-3.22 (m, 2H, CH₂), 3.82-3.95 (q, 2H, CH₂), 7.09-7.24 (m, 4H, C₆H₄).

The hydrochloride, recrystallized from ethanol-diethyl ether, had mp 136-140°.

Anal. Calcd. for $C_{15}H_{23}N \cdot HCl$: C, 70.98; H, 9.53; Cl, 13.97; N, 5.52. Found: C, 70.8; H, 9.69; Cl, 14.0; N, 5.39.

Preparation of 3-(2-Methylphenyl)dibutylamine (10).

N-Butyl-5-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine (9) (2.17 g, 0.01 mole) was hydrogenated in 50 ml of dioxane over 0.1 g of 10% palladium on charcoal at 100° and at 1500 psi in a stainless steel autoclave with efficient stirring for 5 hours. The filtrate obtained from the hydrogenation was evaporated giving a residue of 2.17 g (99%). This compound has the following physical data: ^{1}H-nmr: δ 0.89 (t, 3H, CH₃), 1.20 (d, 3H, CH₃), 1.21-1.45 (m, 4H, CH₂), 1.72-1.83 (m, 2H, CH₂), 2.32 (s, 3H, CH₃), 2.48-2.57 (m, 4H, CH₂), 3.02-3.07 (m, H, CH), 7.05-7.24 (m, 4H, C₆H₄).

The hydrochloride, recrystallized from ethanol-diethyl ether, had mp 135-138°.

Anal. Calcd. for $C_{15}H_{25}N \cdot HCl$: C, 70.42; H, 10.24; Cl, 13.86; N, 5.48. Found: C, 70.2; H, 10.5; Cl, 13.9; N, 5.31.

cis-N-Benzyl-2,6-diethylmorpholine Hydrochloride.

This compound had mp 181-183°.

Anal. Calcd. for $C_{15}H_{23}NO \cdot HCl$: C, 66.77; H, 8.97; Cl, 13.14; N, 5.19. Found: C, 66.5; H, 9.08; Cl, 13.2; N, 5.11.

trans-N-Benzyl-2,6-diethylmorpholine Hydrochloride.

This compound had mp 137-139°.

Anal. Calcd. for $C_{15}H_{23}NO \cdot HCl$: C, 66.7; H, 8.97; Cl, 13.14; N, 5.19. Found: C, 66.6; H, 9.10; Cl, 13.2; N, 5.14.

Preparation of N-Benzyl-N-crotyl-(2-hydroxy-1-butyl)amine (4).

DL-1-Benzylamino-2-butanol [2] (17.9 g, 0.10 mole), 13.6 g (0.15 mole) of trans-crotyl chloride, 20 g (0.2 mole) of triethylamine and 250 ml of toluene were refluxed for 24 hours with efficient stirring. The precipitated triethylamine hydrochloride was filtered off. The solvent was evaporated and the residue distilled to give 21.9 g (94%) of 4 bp 90-95° (0.1 mm). Analysis (glc) showed two isomers (84:16).

Preparation of N-Benzyldicrotylamine (5).

Benzylamine (10.7 g, 0.10 mole), 27.2 g (0.30 mole) of trans-crotyl chloride, 40 g (0.4 mole) of triethylamine and 250 ml of toluene were refluxed for 24 hours with efficient stirring. The isolation of the reaction products was carried out as above. N-Benzyldicrotylamine, (20.5 g, 95%), bp 144-146° (10 mm) was obtained. Analysis (glc) showed three isomers (70:28:2).

Preparation of N-Benzyl-N-crotyl-1-butylamine (6).

N-Benzyl-1-butylamine [15] (16.3 g, 0.10 mole), 13.6 g (0.15 mole) of trans-crotyl chloride, 20 g (0.2 mole) of triethylamine and 250 ml of toluene were refluxed for 24 hours with efficient stirring. The isolation of the reaction products was carried out as above. N-benzyl-N-crotyl-1-butylamine, (20.4 g, 94%), bp 78-82° (0.1 mm), was obtained. Analysis (glc) showed two isomers (86:14).

Preparation of N-Benzyl-N-butyl-(2-hydroxy-1-butyl)amine (8).

N-Benzyl-1-butylamine (32.6 g, 0.20 mole), 18 g (0.25 mole) of 1,2-epoxybutane and 250 ml of 96% ethanol were heated together in a stainless steel autoclave at 150° for 5 hours. The reaction product was distilled to give 45.2 g (96%) of N-benzyl-N-butyl-(2-hydroxy-1-butyl)amine, bp 90-92° (0.1 mm). This compound had the following physical data: ^{1}H-nmr: δ 0.86 (t, 3H, CH₃), 0.94 (t, 3H, CH₃), 1.24-1.48 (m, 6H, CH₂), 2.31-2.59 (m, 4H, CH₂), 3.37-3.83 (q, 2H, CH₂), 3.54-3.61 (m, H, CH), 7.22-7.30 (m, 4H, C₆H₄).

The hydrochloride, recrystallized from ethanol-diethyl ether, had mp 119-121°.

Anal. Calcd. for $C_{15}H_{25}NO \cdot HCl$: C, 66.28; H, 9.64; Cl, 13.04; N, 5.15. Found: C, 66.5; H, 9.70; Cl, 13.2; N, 5.10.

Preparation of N-Benzyl-N-butyl-(3-hydroxy-1-butyl)amine (7).

1-Benzylamino-3-hydroxybutane [16] was prepared from 3-hydroxybutyronitrile [17] by catalytic hydrogenation over Raney-nickel [18] followed by benzoylation and reduction with lithium aluminium hydride [7]. To a mixture of 35.8 g (0.20 mole) 1-benzylamino-3-hydroxybutane, 50 g (0.5 mole) of triethylamine and 500 ml of benzene, 48 g (0.45 mole) of butyryl chloride was slowly added with stirring and efficient cooling. The reaction mixture was refluxed for 1 hour with stirring. The triethylamine hydrochloride formed was filtered off and washed with diethyl ether. The benzene ether solution was slowly added to a slurry of 35 g of lithium aluminium hydride in 1.5 ℓ of diethyl ether. The reaction mixture was refluxed for 5 hours and then decomposed. After filtration the solvents were evaporated and the residue distilled. N-Benzyl-N-butyl-(3-hydroxy-1-butyl)amine (41.4 g, 88%), bp 92-95° (0.1 mm) was obtained. This compound had the following physical data: ^{1}H-nmr: δ 0.86 (t, 3H, CH₃), 1.11 (d, 3H, CH₃), 1.24-1.32 (m, 2H, CH₂), 1.44-1.65 (m, 4H, CH₂), 2.24-2.28 (m, H, CH₂), 2.51-2.58 (m, 2H, CH₂), 2.67-2.73 (m, H, CH₂), 3.23-3.86 (q, 2H, CH₂), 3.83-3.87 (m, H, CH), 7.22-7.30 (m, 4H, C₆H₄).

REFERENCES AND NOTES

[1] To whom correspondence regarding this paper should be addressed.
[2] S. Hernestam, J. Heterocyclic Chem., 20, 1681 (1983).
[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] S. Hernestam and G. Stenvall, ibid., 13, 733 (1976).

[8] W. J. Gensler in "Heterocyclic Compounds", Vol 4, R. C. Elderfield, ed, John Wiley and Sons, Inc., New York, NY, 1952, p 389.

[9] S. D. Venkataramu, G. D. Macdonell, W. R. Purdum, G. A. Dilbeck and K. D. Berlin, *J. Org. Chem.*, **42**, 2195 (1977).

[10] W. L. Mendelson, C. B. Spainhour, Jr., S. S. Jones, B. L. Lam and K. L. Wert, *Tetrahedron Letters*, 1393 (1980).

[11] T. J. Schwan, *J. Heterocyclic Chem.*, **8**, 839 (1971); T. J. Schwan, G. S. Lougheed and S. E. Burrows, *ibid.*, **11**, 807 (1974); T. J. Schwan and G. S. Lougheed, *ibid.*, **12**, 441 (1975).

[12] I. H. Hoffmann, G. Ehrhart and K. Schmitt, *Arzneim.-Forsch.*, **21**, 1045 (1971).

[13] G. Bobowski, J. M. Gottlieb, B. West and J. Shavel, Jr., *J. Heterocyclic Chem.*, **16**, 1525 (1979); G. Bobowski, J. M. Gottlieb and B. West, *ibid.*, **17**, 1563 (1980); G. Bobowski and J. M. Gottlieb, *ibid.*, **19**, 21 (1982).

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

[15] A. Einhorn and H. Pfeiffer, *Ann. Chem.*, **310**, 225 (1900).

[16] J. Lichtenberger and R. Lichtenberger, *Bull. Soc. Chim. France*, 1002 (1948).

[17] G. Heim, *Bull. Soc. Chim. Belg.*, **40**, 201 (1931).

[18] F. Zymalkowski, "Katalytische Hydrierungen im Organisch-Chemischen Laboratorium", Ferdinand Enke Verlag, Stuttgart, 1965, p 264.