Giorgio Chelucci* and Giampaolo Giacomelli

Dipartimento di Chimica, Universita' di Sassari, Via Vienna 2,
07100 Sassari, Italy

Received June 22, 1989

Optically active (+)-(*S*)-5-*sec*-butyl- and (-)-(*S*)-3-*sec*-butyl-2(1*H*)-pyridinone are synthesized and the relationship between optical activity and minimum optical purity of the latter is determined.

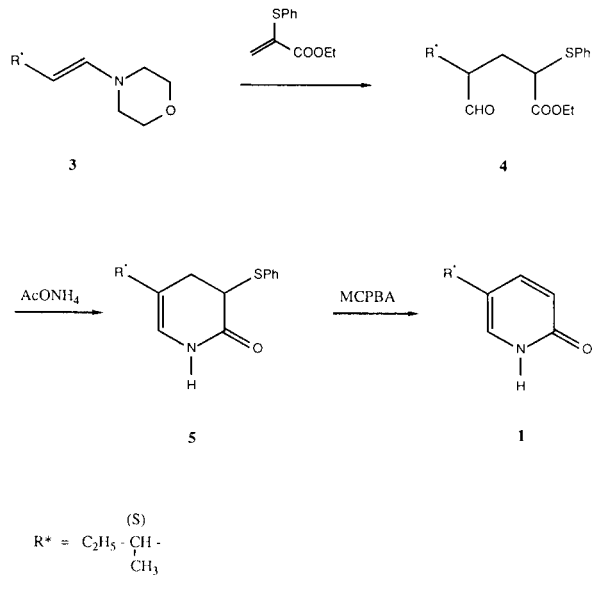
J. Heterocyclic Chem., **27**, 311 (1990).

Pyridinones are very important intermediates in pyridine chemistry, being easily converted into halopyridines from which a number of variously substituted pyridines are available [1]. Moreover, the 2(1*H*)-pyridinone moiety is a prominent structural feature in a number of natural products [2]. With existing methods, highly substituted 2(1*H*)-pyridinones [3] or alkyl-2(1*H*)-pyridinones bearing electron-withdrawing groups [4] are particularly obtainable, while few methods exist for the preparation of monoalkyl-substituted 2(1*H*)-pyridinones [5]. At present only one optically active alkyl-2(1*H*)-pyridinone, in which the asymmetric center of the alkyl substituent is adjacent to the heterocyclic ring has been reported [6].

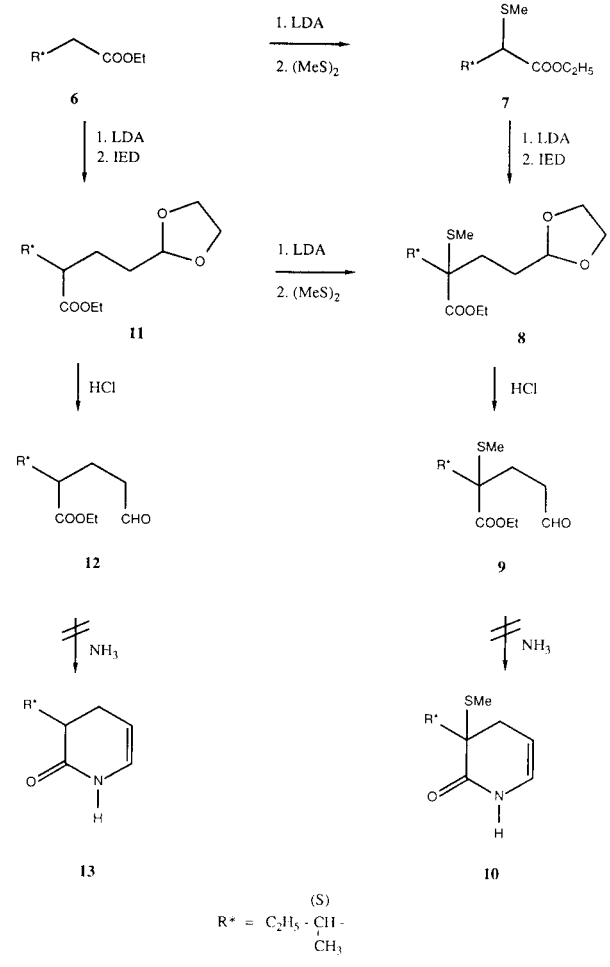
We report here an alternative way of synthesizing (+)-(*S*)-5-*sec*-butyl-2(1*H*)-pyridinone (**1**) [6] and the results obtained in the preparation of the new (-)-(*S*)-3-*sec*-butyl-2(1*H*)-pyridinone (**2**) with the determination of the relationship between its optical activity and minimum optical purity.

The reaction sequence leading to **1** is shown in Scheme I. The piperidino enamine of (-)-(*S*)-3-methylpentanal was allowed to react in acetonitrile with ethyl 2-phenylthiopropenoate [7]. The crude adduct was hydrolyzed to give 65% overall yield of ethyl phenylthio-4-formyl-5-methyleptanoate (**3**). Treating this compound with ammonium acetate gave 2-phenylthio-5-*sec*-butyl-3,4-dihydro-2(1*H*)-pyridinone (**4**) (68%). When a methylene chloride solution of **4** was treated with 3-chloroperbenzoic acid at room temperature, oxidation of the sulfur atom was followed by spontaneous extrusion of sulfenic acid [8] to give the expected (+)-(*S*)-5-*sec*-butyl-2(1*H*)-pyridinone (**1**) in good yield (82%). The rotatary power of **1** was identical to the previously reported maximum rotatory power, indicating that no racemization occurs during the various steps of this synthesis.

Scheme I



Scheme II

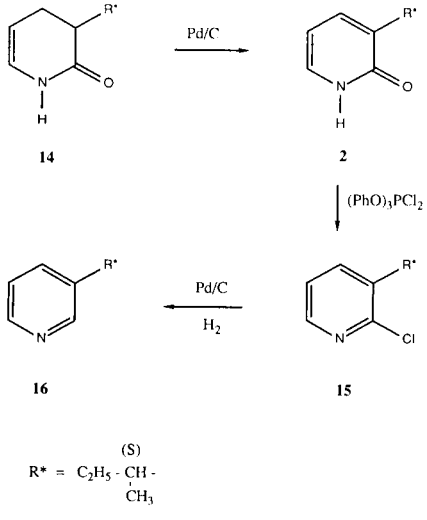


The result obtained in the preparation of **1** prompted us to extend the above synthetic strategy to the preparation of 2(1*H*)-pyridinone **2**. In this case the proper γ-formylester was prepared according to Scheme II. Alkylation with 2-(2-iodoethyl)-1,3-dioxolane of ethyl 2-methylthio-3-methylpentanoate (**5**), obtained by monosulfenylation of ethyl (+)-(*S*)-3-methylpentanoate (**6**) [8], gave a 64% overall yield of the protected γ-formylester **8**. This key intermediate was also obtained in lower yield (28%) by reversing the order of sulfenylation-alkylation (Scheme II). Deprotection of the formyl function of **8** gave the γ-formylester **9** which was treated with ammonium acetate in boiling benzene-acetic acid. Much to our surprise, cyclization of **9** to give the unsaturated pyridinone **10** failed, and although many permutations of conditions were explored (by varying reagents, temperature, solvents *etc.*) in no case could the desired lactam be obtained.

In an attempt to verify whether the thiomethyl substituent present on **9** is responsible for the above results, we submitted ethyl 2-*sec*-butyl-2-(2-formylethyl)pentoanoate (**12**) to the same reaction conditions utilized for the cyclization of **9**. Also in this case positive no results were obtained.

Since it has been recently reported that 3-substituted-3,4-dihydro-2(1*H*)-pyridinones are obtained by cyclization of δ-acetal amides [9], we thought we would utilize this route to prepare the 2(1*H*)-pyridinone **2**. Thus, starting from (+)-(*S*)-3-methylpentanenitrile we prepared the optically active 3-*sec*-butyl-3,4-dihydro-2(1*H*)-pyridinone (**14**) following the procedure reported for the same racemic compound [9]. Compound **14** was dehydrogenated in the presence of palladium metal on charcoal in boiling xylene to give **2** (38%) (Scheme III).

Scheme III



To evaluate the enantiomeric purity of **2**, we chemically correlated it with the known (+)-(*S*)-*sec*-butylpyridine (**16**) [10] (Scheme III). Compound **2** was converted into (-)-(*S*)-2-chloro-3-*sec*-butylpyridine (**15**) by reaction with triphenoxyphosphorus dichloride [11] with a yield of 70%, then the halogen atom was easily removed through hydrogenolysis catalyzed by palladium on charcoal [12]. Compound **16**, obtained in 83% showed $[\alpha]_D^{25}$ +22.23 (cyclohexane); this value is consistent with the reported maximum rotatory power of **16** [10]. This result shows that no loss of optical activity occurs during the various steps of this synthesis.

EXPERIMENTAL

Boiling points are uncorrected. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. The gc controls were effected on a Perkin Elmer 3920 B gas chromatograph, using 2 m x 2 mm column packed with 5% SE-30 on Chromosorb W and opeating at a programmed temperature (between 100 and 300). The ^{1}H nmr spectra were obtained with a Varian T-60 spectrometer in deuteriochloroform solution, unless otherwise stated, using tetramethylsilane as an internal standard (δ = 0). The ir spectra were measured with a Perkin Elmer 1310 spectrophotometer. Elemental analyses were performed on a Perkin Elmer 240 B analyzer.

The preparation of lithium diisopropylamide involves the addition by syringe of 1 equivalent of *n*-butyllithium to a solution of diisopropylamine in THF at -78°. This solution is ready for use after stirring at -78° for 15 minutes.

Materials.

(*S*)-1-Piperidino-3-methyl-1-pentene was prepared according to Chelucci *et al.* [6]. Ethyl 2-phenylthiopropenoate was obtained according to Monteiro *et al.* [13]. 2-(2-Iodoethyl)-1,3-dioxolane (IED) was prepared according to Larson *et al.* [14]. Ethyl (+)-(*S*)-3-methylpentanoate [15], $[\alpha]_D^{25}$ +7.97 (c 1.98, cyclohexane), was prepared from (+)-(*S*)-1-chloro-3-methylbutane [16] by a conventional method [17]. Optically active 3-*sec*-butyl-3,4-dihydro-2(1*H*)-pyridinone was obtained from (+)-(*S*)-3-methylpentanenitrile [18], ($[\alpha]_D^{25}$ +7.66 (neat)), following a described procedure [9].

Ethyl Phenylthio-4-formyl-5-methyleptanoate (**4**).

Ethyl 2-phenylthiopropenoate (18.8 g, 90 mmoles) was added dropwise at 0° to a solution of (*S*)-1-piperidino-3-methyl-1-pentene (15.2 g, 90 mmoles) in anhydrous acetonitrile (90 ml). After stirring for 2 hours at room temperature, the solution was heated under reflux for 12 hours. Then a solution of acetic acid (6 ml) in water (40 ml) was added and the resulting mixture was heated under reflux for 8 hours. After cooling, water (100 ml) was added and the mixture extracted with ether. The ethereal phase was dried over anhydrous sodium sulfate and the solvent evaporated to give an oily residue. Column chromatography of this oil on silica gel (30 g/1 g of the product) and benzene as the eluant gave pure **4**, 18.0 g (65%); ^{1}H nmr: 9.56-9.40 (m, 1H), 7.56-7.00 (m, 5H), 4.07 (q, 2H), 3.60 (m, 1H).

Anal. Calcd. for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84; S, 10.39. Found: C, 66.32; H, 7.58; S, 10.44.

2-Phenylthio-5-*sec*-butyl-3,4-dihydro-2(1*H*)-pyridinone (**5**).

A mixture of **4** (11.1 g, 36 mmoles), ammonium acetate (3.4 g), acetic acid (3.1 ml) and benzene (12 ml) was heated under reflux

for 3 hours. After cooling, the mixture was poured into water (30 ml) and extracted with ether. The ethereal phase was washed with 5% aqueous potassium carbonate and dried over sodium sulfate. After evaporation of the solvent the oily residue crystallized on standing; the crystals were washed with pentane to give pure **5**, 6.4 g (68%), mp 67-68°; ^{1}H nmr: 9.5-9.2 (broad, 1H), 9.13-8.87 (m, 1H), 7.60-7.00 (m, 5H), 5.90-5.67 (m, 1H), 3.67 (t, 1H); ir (potassium bromide): 1665 cm^{-1}.

Anal. Calcd. for $C_{15}H_{19}NOS$: C, 68.93; H, 7.33; N, 5.36; S, 12.27. Found: C, 68.73; H, 7.56; N, 5.46; S, 12.29.

(+)-(*S*)-5-*sec*-Butyl-2(1*H*)-pyridinone (**1**).

A solution of 3-chloroperbenzoic acid (1.1 g of 85% mixture, 5.5 mmoles) in methylene chloride (50 ml) was added dropwise to a solution of **5** (1.3 g, 5 mmoles) in methylene chloride (50 ml). Upon completion of the addition, tlc analysis (7:3 benzene-acetone) showed complete loss of the starting material spot. The reaction mixture was poured into 10% aqueous sodium sulfite solution (100 ml). The organic phase was separated, washed with saturated aqueous sodium bicarbonate, dried and concentrated *in vacuo* to give an oily residue. This material was chromatographed on silica gel using benzene and then methanol as the eluents to yield pure **1**, 0.62 g (82%), bp 98° (0.02 mm Hg), $[\alpha]_D^{25}$ +31.13 (c 1.06, absolute ethanol). Analytical and spectral data were identical with an authentic sample [6].

Ethyl 2-Methylthio-3-methylpentanoate (**7**).

A solution of ethyl (+)-(*S*)-3-methylpentanoate (5.76 g, 40 mmoles) in THF (50 ml) was added dropwise at -78° to a solution of lithium diisopropylamide (42 mmoles) in THF (80 ml). After 1 hour this solution was added *via* a syringe into a solution of dimethyl disulfide (4.52 g, 48 mmoles) in THF (50 ml) at room temperature. The resulting solution was stirred at room temperature for 1 hour and then treated with water. The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated and the residue purified by fractional distillation to give pure **7**, 6.1 g (80%), bp 96° (8 mm, Hg); ^{1}H nmr: 4.13 (q, 2H), 2.87 (d, 2H), 2.07 (s, 3H).

Anal. Calcd. for $C_9H_{18}O_2S$: C, 56.80; H, 9.53; S, 16.85. Found: C, 56.65; H, 9.73; S, 19.96.

Ethyl 2-*sec*-Butyl-2-methylthio-5,5-ethylenedioxypentanoate (**8**).

A solution of **7** (6.84 g, 36 mmoles) in THF (10 ml) was added at -78° to a solution of lithium diisopropylamide (43 mmoles) in THF (80 ml) and HMPT (14.4 ml). The resulting mixture was stirred at -78° for 1 hour and then a solution of IED (9.8 g, 43 mmoles) in THF (20 ml) was added dropwise. After 1 hour to -78° the solution was allowed to rise slowly room temperature and then treated with water. The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated and the residue purified by fractional distillation to give pure **8**, 8.32 g (80%), bp 130° (0.2 mm, Hg); ^{1}H nmr: 4.78-4.60 (m, 1H), 4.20 (q, 2H), 3.88-3.70 (m, 4H), 2.00 (s, 3H), 1.24 (t, 3H).

Anal. Calcd. for $C_{14}H_{26}O_4S$: C, 57.90; H, 9.02; S, 11.04. Found: C, 57.62; H, 9.12; S, 11.33.

Ethyl 2-*sec*-Butyl-2-(2-formylethyl)-2-methylthiopentanoate (**9**).

A mixture of **8** (5.5 g, 19 mmoles), acetone (200 ml) and 25% aqueous hydrochloric acid (36 ml) was heated under reflux for 24 hours. The acetone was distilled off and the residue extracted with ether. The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated and the residue purified by fractional distillation to give pure **7**, 3.4 g (73%), 110° (0.3 mm, Hg); ^{1}H nmr: 9.73 (s, 1H), 4.16 (q, 2H), 2.03 (s, 3H), 1.23 (t, 3H).

Anal. Calcd. for $C_{12}H_{22}O_3S$: C, 58.50; H, 9.00; S, 13.01. Found: C, 58.70; H, 9.18; S, 13.20.

Ethyl 2-*sec*-Butyl-5,5-ethylenedioxypentanoate (**11**).

A solution of ethyl (+)-(*S*)-3-methylpentanoate (7.92 g, 55 mmoles) in THF (20 ml) was added at -78° to a solution of lithium diisopropylamide (60 mmoles) in THF (70 ml). The resulting mixture was stirred at -78° for 1 hour and then a solution of IED (12.64 g, 55 mmoles) and HMPT (4 ml) in THF (20 ml) was added dropwise. After 1 hour at -78° the solution was allowed to obtain room temperature slowly and then treated with water. The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated and the residue purified by fractional distillation to give pure **11**, 9.4 g (70%), 100° (0.3 mm, Hg); ^{1}H nmr: 4.83-4.66 (m, 1H), 4.13 (q, 2H), 3.90-3.70 (m, 4H), 1.23 (t, 3H).

Anal. Calcd. for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.79; H, 9.99.

Preparation of **8** from **11**.

A solution of **11** (0.61 g, 2.5 mmoles) in THF (5 ml) was added dropwise at -78° to a solution of lithium diisopropylamide (5.3 mmoles) in THF (80 ml). After 15 minutes at -78°, the solution was warmed at -30° and stirring continued for 2.5 hours. To this solution was added dimethyldisulfide (0.574 g, 6.1 mmoles). After 30 minutes at -30° and 2.5 hours at 0°, the solution was treated with water. The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated and the residue purified by fractional distillation to give pure **8**, 0.34 g (47%).

Ethyl 2-*sec*-Butyl-2-(2-formylethyl)pentoanoate (**12**).

A mixture of **11** (2.34 g, 10 mmoles), acetone (100 ml) and 25% aqueous hydrochloric acid (18 ml) was heated under reflux for 24 hours. The acetone was distilled off and the residue extracted with ether. The organic phase was dried over anhydrous sodium sulfate, the solvent evaporated and the residue purified by fractional distillation to give pure **9**, 1.56 g (78%), 95° (0.4 mm, Hg); ^{1}H nmr: 9.70 (s, 1H), 4.20 (q, 2H), 1.24 (t, 3H).

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 69.96; H, 10.07. Found: C, 69.76; H, 10.20.

(-)-(*S*)-3-*sec*-Butyl-2(1*H*)-pyridinone (**2**).

A mixture of optically active 3-*sec*-butyl-3,4-dihydro-2(1*H*)-pyridinone (**14**) (2,3 g, 15 mmoles) and 10% palladium on charcoal (0.6 g) in xylene (20 ml) was heated under reflux for 15 minutes. After cooling the mixture was filtered and the solvent removed *in vacuo*. The residue was chromatographed on silica gel and ether as the eluent to give pure **2**, 0.86 g (38%), mp 75°; $[\alpha]_D^{25}$ -13.99 (c 2.08, absolute ethanol); ^{1}H nmr: 7.26 (d, 2H), 6.22 (t, 1H), 3.05 (m, 1H), 1.60 (m, 2H), 1.13 (d, 3H), 0.83 (t, 3H).

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.10; H, 8.90; N, 9.06.

(+)-(*S*)-Chloro-5-*sec*-butylpyridine (**15**).

Compound **2** (0.41 g, 2.7 mmoles) was added to a mixture of phosphorus pentachloride (0.57 g, 2.7 mmoles) and phenol (0.76 g, 8.1 mmoles) previously heated at 100° for 5 hours. The mixture was heated at 100° for an additional 5 hours; after this time, the resulting adduct was decomposed by heating at 250° for 15 minutes. The mixture was extracted with ether. The organic

phase was washed with 5% aqueous sodium hydroxide and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by fractional distillation to give pure **12**, 0.32 g (70%), bp 120° (10 mm, Hg), $[\alpha]_D^{25}$ +6.48 (c 2.2, absolute ethanol); ^{1}H nmr: 8.13 (dd, 1H), 7.50 (dd, 1H), 7.13 (dd, 1H), 3.15 (m, 1H), 1.57 (m, 1H), 1.20 (d, 3H), 0.85 (t, 3H).

Anal. Calcd. for $C_9H_{12}ClN$: C, 63.72; H, 7.13; Cl, 20.90; N, 8.26. Found: C, 63.93; H, 7.23; Cl, 21.03; N, 8.16.

(+)(*S*)-3-*sec*-Butylpyridine (**16**).

A mixture of **15** (253 mg, 1.5 mmoles) and sodium acetate (125 mg) in methanol (20 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal (150 mg). After 12 hours the hydrogen absorption had stopped, the suspension was filtered and the filtrate was acidified with 5% aqueous hydrochloric acid; the solvent was evaporated and the residue made strongly alkaline with 10% aqueous sodium hydroxide. Extraction with ether, drying over anhydrous sodium sulfate, removal of the solvent and distillation at reduced pressure gave pure **13**, 180 mg (83%), bp 70° (10 mm, Hg), $[\alpha]_D^{25}$ +22.23 (c 2.06, cyclohexane). Compound **13** resulted identical with an authentic sample [10].

Acknowledgement.

This work was financially supported by the Ministero della Pubblica Istruzione and by the Regione autonoma Sardegna.

REFERENCES AND NOTES

[1b] B. C. Uff in "Comprehensive Heterocyclic Chemistry", Vol **2**, Part 2A, A. J. Boulton and A. McKippop, eds, Pergamon Press, New York, 1984 pp 359-364; [b] T. W. Bell, L. Y. Hu and S. V. Patel, *J. Org. Chem.*, **52**, 3847 (1987); [c] T. Rode and E. Breitmaier, *Synthesis*, 574 (1987); [d] J. W. Tilley and S. Zawoiski, *J. Org. Chem.*, **53**, 387 (1988).

[2a] D. Lednicer and L. A. Mitscher, "The Organic Chemistry of Drug Synthesis", Wiley, New York, NY, 1977, Vol **1**; 1980, Vol **2**; [b] M. F. Grundon, "The Chemistry of the Alkaloids", Chemical Society, London, 1977, Vol **7** and earlier volumes of this series.

[3] J. H. Rigby and N. Balasubramanian, *J. Org. Chem.*, **54**, 224 (1989).

[4] G. Jones, in "Comprehensive Heterocyclic Chemistry", Vol **2**, Part 2A, A. J. Boulton and A. McKippop, eds, Pergamon Press, New York, 1984 pp 395-510.

[5a] L. E. Overman, S. Tsuboi, J. P. Roos and G. F. Taylor, *J. Am. Chem. Soc.*, **102**, 747 (1980) and references therein; [b] J. Yamamoto, M. Imagawa, S. Yamauchi, O. Nakazawa and M. Umezu, *Tetrahedron*, **37**, 1871 (1981).

[6] G. Chelucci, M. Marchetti, C. Botteghi and F. Soccolini, *J. Heterocyclic Chem.*, **21**, 1717 (1984).

[7] R. Gregge, J. L. Hermann and R. H. Schessinger, *Tetrahedron Letters*, 2603 (1973).

[8] B. M. Trost, *Chem. Rev.*, **78**, 363 (1978).

[9] G. Chelucci and G. Giacomelli, *J. Heterocyclic Chem.*, in press.

[10] G. Asara, C. Botteghi, S. Gladiali and F. Soccolini, *Synth. Commun.*, **9**, 69 (1979).

[11] D. G. Coe, H. N. Rydon and B. L. Tonge, *J. Chem. Soc.*, 323 (1957).

[12] J. P. Wibaut and E. C. Kooyman, *Rec. Trav. Chim.*, **63**, 231 (1944).

[13] H. J. Monteiro and A. L. Gemal, *Synthesis*, 437 (1975).

[14] L. Larson and R. Klesse, *J. Org. Chem.*, **50**, 3627 (1985).

[15] I. G. Vasi and K. R. Desai, *J. Inst. Chem.*, **44**, 77 (1972).

[16] P. Pino, L. Lardicci and L. Centoni, *Gazz. Chim. Ital.*, **91**, 428 (1961).

[17] J. Houben, *Ber.*, **36**, 3087 (1903).

[18] W. Kirme, W. Gruber and J. Knist, *Chem. Ber.*, **106**, 1376 (1973).