Tetrahedron Vol. 45, No. 12, pp. 3907 to 3922, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

PREPARATION OF PIPERIDINES FROM δ-CHLOROIMINES

PAUL SULMON[£], NORBERT DE KIMPE* and NICEAS SCHAMP

Laboratory of Organic Chemistry, Faculty of
Agricultural Sciences, State University of Gent,
Coupure links 653, B-9000 Gent, Belgium

(*Received in UK* 17 *January* 1989)

Abstract

The reaction of δ-chloro imines with various nucleophiles e.g. metal hydrides, potassium cyanide, alcohols and alkoxides gave rise to piperidines, 2-cyanopiperidines and 2-alkoxypiperidines respectively. These piperidines were formed by the addition of the nucleophile across the carbon-nitrogen double bond followed by intramolecular nucleophilic substitution.

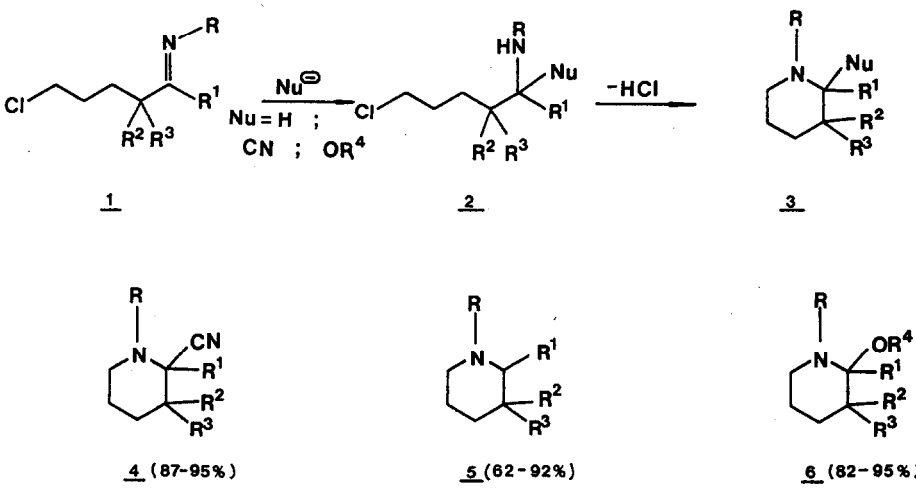
Introduction

The piperidine alkaloids[1-5] are a group of compounds widespread in nature. Piperidines were already isolated from several animals and plants but the best known natural piperidines are secondary plant metabolites such as coniine, pinidine, isopelletierine, sedamine, anaferin, etc...[6-14] Most of the piperidines isolated from nature are substituted at the 2-, 3- and/or 6-position and sometimes on nitrogen. The chemistry of a group of piperidines which is rapidly growing during the last two decades, due to their applications, is the group of the sterically hindered piperidines[1]. Some hindered amines are local anaesthetics (eucaine) while others have other pharmacological properties[1]. Some hindered piperidines are also polymerisation inhibitors and thermo- and photostabilizers[1]. The preceding facts amply demonstrate the importance of piperidines in modern organic chemistry. Therefore, novel entries in the area of these 6-membered nitrogen-containing compounds still deserve attention. Herein we describe the synthesis of functionalized piperidines from δ-chloroimines.[15]

Results and discussion :

δ-Chloroimines 1 were prepared by base-induced α-alkylation of imines with α,ω-dihalopropanes[15]. Reaction of δ-chloroimines 1 with nucleophiles such as potassium cyanide, complex metal hydrides, alcohols and alkoxides lead to 2-cyanopiperidines 4, piperidines 5 and 2-alkoxypiperidines 6, respectively (Scheme I). The piperidines 4, 5 and 6 are formed by ring closure of adducts 2, which are produced by addition of the nucleophile across

the imino function of δ-chloroimines 1 (Scheme I). The reaction of δ-chloroimines with these nucleophiles is fairly general in as much that this reaction provides an elegant approach to piperidines. According to a similar set of mechanisms, it is worthwhile to mention that β-haloimines[16] produce 2-functionalized azetidines on reaction with nucleophiles[17,18].



SCHEME I

The reaction of δ-chloroimines 1 with potassium cyanide in methanol was complete after several hours at reflux and lead to 2-cyanopiperidines 4 in 87-95% yield (Table 1, entry 1-5). All the 2-cyanopiperidines described are new compounds, the spectral data of which are compiled in Tables II and III. In order to test the possibility to prepare 2-cyanopiperidines 4 without substituents at the 3-position, δ-chloroimine 1e (R=i-Pr, $R^1=C_6H_5$, R^2=H, R^3=H) was reacted with potassium cyanide in methanol. Unfortunately, 2-cyanopiperidine 4e could not be isolated after the normal workup procedure. 2-Cyanopiperidine 4e was initially formed (90% crude yield) on reaction of δ-chloroimine 1e with potassium cyanide in methanol (Scheme II). However, heating of 2-cyanopiperidine 4e (distillation or gas chromatographic analysis) caused elimination of hydrogen cyanide to produce cyclic enamine 7. The greater stability of 2-cyanopiperidines 4a-d originates from the impossibility to eliminate hydrogen cyanide due to the presence of the alkyl substituents at the 3-position. The synthesis of the azaheterocycle 7 is comparable to the synthesis of endocyclic enamine 11 through alkylation of imines 9 with α,ω-dihalopropanes (the resulting intermediate δ-haloimines

Table I : Synthesis of Substituted Piperidines 4, 5 and 6.

entry	Starting Compound	R	R^1	R^2	R^3	Reaction Conditions[a]	Yield (%)
1	1a	i-Pr	H	Me	Me	KCN (2E)/MeOH (10%) Δ 1h	4a:89[b]
2	1b	t-Bu	H	Me	Me	KCN (2E)/MeOH (10%) Δ 3h	4b:95[b]
3	1c	$CH_2C_6H_5$	H	Me	Me	KCN (2E)/MeOH (10%) Δ 6h	4c:91[b]
4	1d	t-Bu	H	Me	H	KCN (2E)/MeOH (10%) Δ 3h	4d:87[b]
5	1e	i-Pr	C_6H_5	H	H	KCN (2E)/MeOH (10%) Δ 20h	4e:90[c]
6	1a	i-Pr	H	Me	Me	LAH (8E)/ether (10%) Δ 2h	5a:65-87[d]
7	1b	t-Bu	H	Me	Me	LAH (8E)/ether (10%) Δ 2h	5b:82[b]
8	1c	$CH_2C_6H_5$	H	Me	Me	LAH (8E)/ether (10%) Δ 5h	5c:91[b]
9	1d	t-Bu	H	Me	H	LAH (8E)/ether (10%) RT 2h	5d:0[e]
10	1d	t-Bu	H	Me	H	LAH (8E)/ether (10%) Δ 8d	5d:92[b]
11	1e	i-Pr	C_6H_5	H	H	LAH (8E)/ether (10%) Δ 5h	5e:62[f]
12	1a	i-Pr	H	Me	Me	MeOH (10%) Δ 3h	6a:82[b]
13	1a	i-Pr	H	Me	Me	KSCN (2E)/MeOH (10%) Δ 3h	6a:90[b]
14	1a	i-Pr	H	Me	Me	NaOMe/MeOH (2E/2N) Δ 1h	6a:95[b]
15	1a	i-Pr	H	Me	Me	NaOi-Pr/HOi-Pr (2E/1N) Δ 3h	6c:87[b]
16	1b	t-Bu	H	Me	Me	MeOH (10%) Δ 3h	6b:87[b]
17	1b	t-Bu	H	Me	Me	NaOMe/MeOH (2E/2N) Δ 2h	6b:93[b]

a : KCN = potassium cyanide; LAH = lithium aluminium hydride; E = equivalents; N = normal; Δ = reflux; h = hour(s); d = day(s); 10% = 10% solution (W/V starting material/solvent); RT = room temperature.
b : These compounds were not distilled but were free of impurities (purity > 96%; checked by GLC and ^{1}H-NMR).
c : Compound 4e is transformed into 7 by distillation (125-130°C/11 mm Hg) or by preparative GLC.
d : Bp. 50-55°C/11 mm Hg.
e : Only compound 17d was isolated.
f : Also 30% of compound 17e is present (17e : mp. 130°C).

Table II : Spectral Data (IR, ^{1}H-NMR, MS) of Piperidines 4, 5 and 6.

Compound	IR (NaCl) (cm^{-1})	^{1}H-NMR (δ)	Mass Spectrum (70eV) m/e (%)
4a	$\nu_{C\equiv N}$:2222	($CDCl_3$): 1.12 (6H,s,C(CH_3)$_2$); 3.45 (1H,s,br,CHCN); 1.07 and 1.13 (6H,2xd,J=6.5Hz,CH(CH_3)$_2$); 1.20-3.00 (7H,m,(CH_2)$_3$ and CH(CH_3)$_2$).	180(M^+,9); 166(13); 165(100); 111(11); 83(9); 69(16); 56(11); 55(17); 43(21); 42(15); 41(33); 39(10).
4b	$\nu_{C\equiv N}$:2220	($CDCl_3$): 1.08 (6H,s,(CH_3)$_2$C); 1.15 (9H,s,t-Bu); 3.60 (1H,s,br,CHCN); 1.20-3.20 (6H,m,(CH_2)$_3$).	194(M^+,7); 180(14); 179(100); 152(8); 96(9); 83(8); 70(8); 69(18); 68(9); 58(18); 57(38); 56(20); 55(21); 43(8); 42(16); 41(44); 40(96); 39(11).
4c	$\nu_{C\equiv N}$:2221	($CDCl_3$): 1.03 (3H,s,CH_3); 1.09 (3H,s,CH_3); 1.00-3.00 (6H,m,(CH_2)$_3$); 3.22 (1H,s,br,CHCN); 3.50 and 3.70 (2H,2xd,AB-system,J=13.2 Hz,$CH_2C_6H_5$); 7.33 (5H,s,C_6H_5).	228(M^+,12); 159(14); 137(47); 92(15); 91(100); 83(18); 69(10); 65(13); 56(12); 55(26); 43(9); 41(29); 40(12).

4d	$\nu_{C\equiv N}$: 2221	(CCl_4): 1.13 (9H,s, $(CH_3)_3$); 0.98 (3H,d,J=6.5 Hz,CH_3C); 1.00-4.20 (8H, m,$(CH_2)_3$ and CHCN and CH CH_3).	180(M^+,6); 166(13); 165(100); 153(9); 138(33); 98(17); 97 (14); 96(18); 83(15); 82(31); 81(17); 80(7); 70(17); 69(18); 68(15); 67(8); 58(33); 57(87); 56(19); 55(21); 54(7); 53(9); 43(14); 42(29); 41(96); 40(8); 39(23).
5a	-	($CDCl_3$): 0.93 (6H,s, $(CH_3)_2$); 0.97 (6H,d,J=6.5 Hz,$CH(CH_3)_2$); 1.00-1.80 (4H,m,$(CH_2)_2$); 2.08 (2H,s, CH_2N); 2.71 (1H,septet,J= 6.5Hz,$CH(CH_3)_2$); 2.20-2.50 (2H,m,CH_2N).	no M^+; 140(10); 107(22); 105 (11); 79(8); 77(8); 72(64); 57 (7); 56(24); 55(12); 44(11); 43(14); 41(15); 40(100).
5b	-	($CDCl_3$): 0.89 (6H,s, $(CH_3)_2$); 0.98 (9H,s,C $(CH_3)_3$); 1.00-1.80 (4H,m, $(CH_2)_2$); 2.09 (2H,s,CH_2-N); 2.40 (2H,t,J=5.8Hz, CH_2N).	169(M^+,16); 155(20); 154(100); 112(9); 98(10); 86(24); 70 (22); 58(21); 57(33); 56(21); 55(42); 44(48); 43(17); 42 (15); 41(36).
5c	-	($CDCl_3$): 0.94 (6H,s, $(CH_3)_2$); 1.00-1.90 (4H,m, $(CH_2)_2$); 2.01 (2H,s,CH_2N); 2.33 (2H,t,J=5.5Hz,CH_2N); 3.41 (2H,s,$CH_2C_6H_5$); 7.24 (C_6H_5).	203(M^+,16); 202(10); 134(29); 126(9); 112(13); 92(8); 91 (81); 65(12); 58(20); 55(17); 43(100); 42(19); 41(20); 39 (14).
5d	-	($CDCl_3$): 0.84 (6H,d,J=6Hz, CH_3CH); 1.05 (9H,s,C $(CH_3)_3$); 1.20-2.30 (7H,m, $(CH_2)_3CH$); 2.80-3.20 (2H, m,CH_2).	155(M^+,9); 141(13); 140(100); 83(9); 71(7); 70(13); 69(10); 58(22); 57(20); 56(13); 55 (34); 44(9); 43(13); 42(14); 41(32); 40(21); 39(9).
5e	-	($CDCl_3$): 0.72 and 0.94 (6H,2xd,J=6Hz,$CH(CH_3)_2$); 1.00-3.40 (9H,m,$(CH_2)_4$ CH); 2.75 (1H,septet,J= 6Hz,$CH(CH_3)_2$); 7.22 (6H,s, C_6H_5).	203(M^+,14); 189(23); 188(100); 126(29); 117(16); 109(18); 107 (16); 104(14); 91(27); 58(54); 56(19); 55(18); 44(14); 42 (20); 41(25); 40(23).
6a	-	(CCl_4): 0.80-2.00 (4H,m, CH_2-CH_2-CH_2N); 2.00-2.80 (2H,m,CH_2N); 0.88 and 0.95 (6H,2xs,$(CH_3)_2C$); 1.02 and 1.06 (6H,2xd,J=6.6Hz,CH $(CH_3)_2$); 2.89 (1H,septet, J=6.6Hz,$CH(CH_3)_2$); 3.35 (3H,s,OCH_3); 3.47 (1H,s, $CHOCH_3$).	185(M^+,13); 170(22); 156(25); 154(65); 153(29); 139(15); 138 (100); 114(41); 113(18); 112 (20); 100(25); 98(16); 96(17); 86(44); 83(16); 82(47); 72 (36); 71(14); 70(15); 68(13); 67(17); 58(20); 57(14); 56 (76); 55(50); 44(18); 43(71); 42(36); 41(88); 40(50); 39 (29).
6b	-	($CDCl_3$): 0.80-2.00 (4H,m, CH_2-CH_2-CH_2-N); 2.60-2.90 (2H,m,CH_2N); 0.93 and 0.96 (6H,2xs,$(CH_3)_2C$); 1.13 (9H, s,$C(CH_3)_3$); 3.43 (3H,s, OCH_3); 3.87 (1H,s,$CHOCH_3$).	-

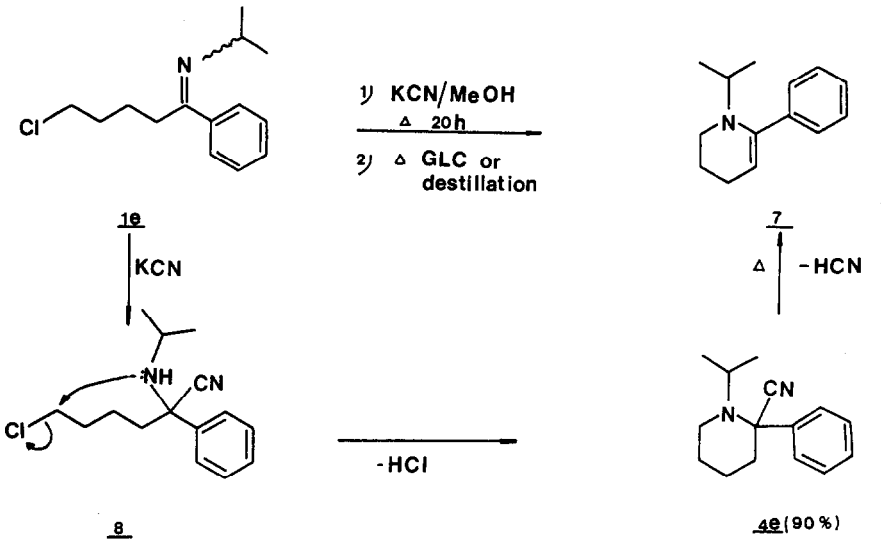
6c	-	($CDCl_3$): 0.80-2.00 (4H,m, CH_2-CH_2CH_2N); 2.00-2.80 ($2H$,m,CH_2N); 0.70-1.30 (18H,m,$NCH(CH_3)_2$,OCH $(CH_3)_2$ and $C(CH_3)_2$); 2.99 (1H,septet,J=6.4Hz,NCH); 3.70 (1H,septet,J=6.2Hz, OCH); 3.76 (1H,s,CH-O-CH $(CH_3)_2$).	no M^+; 169(15); 155(17); 154 (100); 140(16); 138(23); 114 (23); 113(28); 112(48); 100 (21); 98(18); 96(15); 86(15); 84(27); 83(22); 82(23); 72 (31); 70(32); 69(21); 58(33); 57(18); 56(50); 55(51); 45 (32); 44(25); 43(74); 42(31); 41(63); 39(20).

Table III : ^{13}C-NMR Spectral Data of Piperidines 4, 5 and 6.

Compound	C≡N (s)	CR^1	CR^2R^3	if R^2=R^3=CH_3 $C(CH_3)_2$ (q)	N-C	$-(CH_2)_3-$ (t)	R=t-Bu $(CH_3)_3C$ (q)	R=i-Pr $(CH_3)_2CH$ (q)	Other signals
4a	117.5	61.0 (d)	33.5 (s)	28.3; 24.7	53.5 (d)	44.9; 34.1 21.8	-	20.1; 19.8	-
4b	119.1	57.7 (d)	33.8 (s)	28.3; 24.5	54.3 (s)	41.8; 34.0; 22.3	27.0	-	-
4c	115.6	62.8 (d)	33.2 (s)	28.5; 24.3	60.4 (t)	49.1; 33.7; 21.3	-	-	137.3(s,Cq); 128.7;128.4 and 127.5(3x d;Co,Cm and Cp)
4d	118.5	53.8 (d)	35.1 (d)	- -	54.7 (s)	41.8; 26.0; 18.5	27.1	-	29.3(q,CH_3CH)
5a	-	60.3 (t)	30.6 (s)	27.5	54.6 (d)	50.6; 38.2; 23.1	-	18.0	-
5b	-	58.9 (t)	30.8 (s)	27.5	53.1 (s)	46.9; 38.3; 23.7	26.3	-	-
5c	-	65.9 (t)[a]	30.9 (s)	27.3	63.3 (t)[a]	54.7; 37.7; 22.6	-	-	139.4(s,Cq); 128.6;128.0 and 126.6(3x d;Co,Cm and Cp)
5d	-	54.6 (t)	33.5 (d)[a]	-	53.8 (s)	46.3; 31.9[a]; 26.5	26.1	-	20.1(q,CH_3CH)
5e	-	66.1 (d)	26.4 (t)[a]	-	48.3 (d)	44.2; 37.3; 25.6[a]	-	21.3; 12.1	145.5(s,Cq); 128.3;127.5 and 126.6(3x d;Co,Cm and Cp)
6a	-	101.0 (d)	36.2 (s)	27.4; 25.8	53.4 (d)	38.9; 33.0; 22.2	-	21.2; 20.0	59.0(q,OCH_3)
6b	-	96.6 (d)	36.6 (s)	28.1; 25.8	53.2 (s)	38.5; 32.7; 22.7	28.3	-	58.1(q,OCH_3)
6c	-	95.8 (d)	35.7 (s)	28.2; 26.1	52.8 (d)	38.5; 33.2; 22.6	-	22.3[a]; 20.3[a]	69.5(d,OCH $(CH_3)_2$);23.4[a] and 22.8[a](d, $OCH(CH_3)_2$)

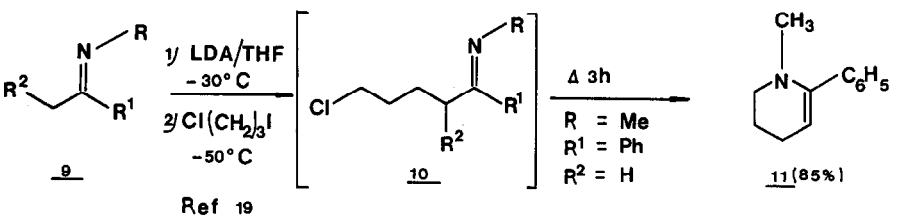
a : or vice versa

10 were not isolated) and subsequent ring closure[19]. The method for the preparation of cyclic enamines, described by D.A. Evans,[19] thus involves the direct cyclisation of in situ generated δ-chloroimines while our method for



SCHEME II

the preparation of enamine 7 concerns the transformation of isolated δ-chloroimine 1e into enamine 7 via a cyanation-dehydrocyanation process.

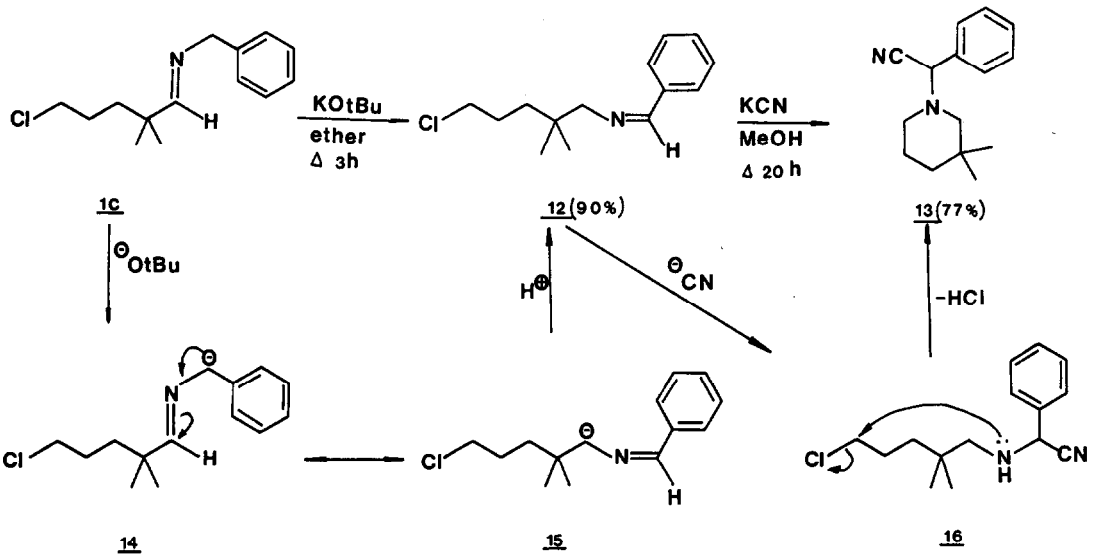


SCHEME III

A related synthesis of piperidines was found in the following way. Base-induced isomerisation of δ-chloroimine 1c with potassium t-butoxide in ether

produced benzylidenamine 12, which underwent cyanide addition and ring closure to afford piperidine 13 (77% yield), bearing the cyano function in the nitrogen substituent (Scheme IV).

2-Cyanopiperidines have already been reported in the literature several times. They were prepared by addition of hydrogen cyanide or cyanide to 1,4,5,6-tetrahydropyridines[20-23] or by addition of cyanide to 3,4,5,6-tetra-



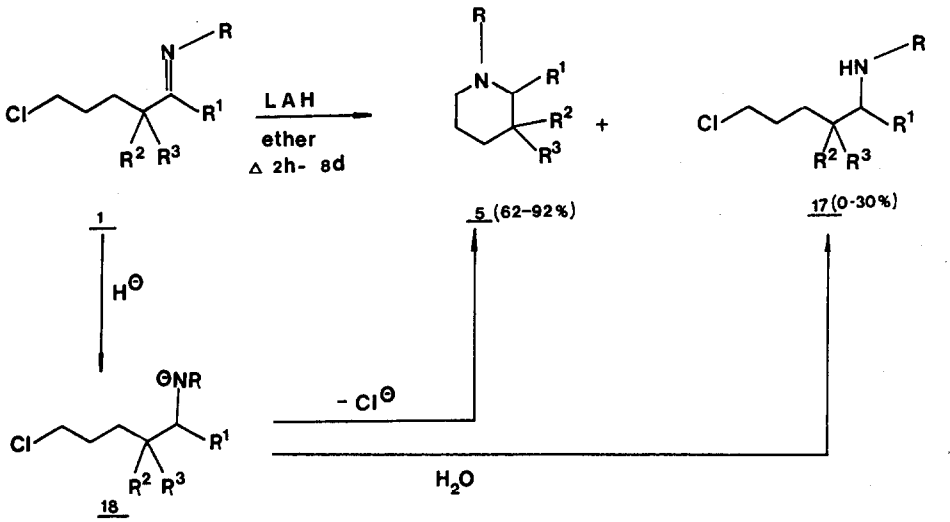
SCHEME IV

hydropyridinium salts[24-31]. 2,6-Dicyanopiperidines were prepared by reaction of glutaraldehyde with a primary amine followed by reaction with potassium cyanide[32-34]. 2-Cyanopiperidines are a useful group of compounds in synthetic organic chemistry because they can be transformed into a variety of natural products,[35-39] such as lysine and piperidine alkaloids.

On reaction of δ-chloroimines 1 with lithium aluminium hydride, piperidines 5 were produced in good to high yields (62-95%). The reaction mechanism for the formation of piperidines 5 is also initiated by the nucleophilic addition of hydride across the carbon-nitrogen double bond followed by ring closure of the intermediate adduct 18 (Scheme V). It must be noticed that, depending upon the reaction conditions, the ring closure is not always complete, especially when the reaction was performed at room temperature (Table I, entry 9) or when a sterically hindered δ-chloroimine was used (Table I, entry 11). In both cases, ω-chloroamines 17 were isolated as

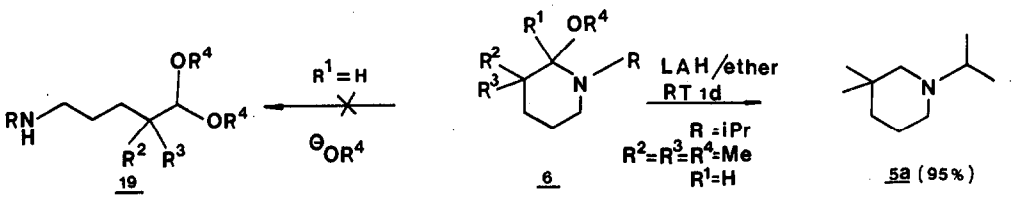
important side products (Table I).

The reaction of δ-chloro imines 1 with alcohols or with nucleophilic bases, such as potassium thiocyanate, sodium methoxide or sodium isopropoxi-



SCHEME V

de in appropriate alcohols gave rise to 2-alkoxypiperidines 6. The same reaction mechanism is applicable as described above for the preparation of piperidines 4 and 5. In contrast with the reaction of β-chloroimines with



SCHEME VI

alcohols,[18] by which the intermediate 2-alkoxyazetidines were opened into the corresponding β-(alkylamino)acetals, the 2-alkoxypiperidines 6 were stable and could be isolated without any problem (Table I). 2-Alkoxypiperidi-

nes reacted with lithium aluminium hydride to form the corresponding piperidines 5. For example, on reaction of 1-isopropyl-2-methoxy-3,3-dimethylpiperidine 6a, prepared according to the procedure described above, with lithium aluminium hydride in ether, 1-isopropyl-3,3-dimethylpiperidine 5a was isolated in 95% yield (Scheme VI).

All piperidines 5 are new compounds, except compound 5d, which was already prepared by reduction of the carbonyl function of 1-t-butyl-3-methyl-4-piperidone[40-42]. On the contrary, 2-alkoxypiperidines 6 are not so well-known in the literature. They were already synthesized by anodic alkoxylation of 1-substituted piperidines[43-49], by addition of alcohols to Δ^1-piperideïnium salts[50] or by nucleophilic substitution of 2-chloropiperidines by methanol[51-53].

All piperidines 5 and 2-alkoxypiperidines 6 are described in Tables II and III.

In conclusion, the reaction of δ-chloro imines with cyanide, hydride, alcohols and alkoxides leads to the formation of piperidines in high yield and can be considered as a valuable synthetic route for these heterocycles. The synthesis of piperidines from δ-chloroimines was verified by using mostly N-isopropyl and N-t-butyl derivates. However, also N-benzyl piperidines (e.g. 4c, 5c) were prepared which underlines the potential of further removal of the N-substituent, if desired. Also the N-benzyl isomerized ring closure of 1c via 12 into 13 offers a vehicle for removal of the N-substituent.

Experimental Section

Infrared spectra were recorded with a Perkin Elmer model 1310 spectrophotometer while ^{1}H-NMR spectra were measured with a Varian T-60 (60 MHz) spectrometer. ^{13}C-NMR spectra were taken on Varian FT 80 (20 MHz) or Bruker WH-360 FT (50 MHz) spectrometers. Mass spectra were obtained from a Varian MAT 112 mass spectrometer (direct inlet system or GC-MS coupling; 70 eV).

Preparation of δ-chloroimines 1

δ-Chloroimines 1 were prepared according to our previously published method[15], namely by α-alkylation of an imine with 1-bromo-3-chloropropane.

Synthesis of 2-cyanopiperidines 4 (General Procedure)

A solution of 0.01 mol of δ-chloroimine 1 in dry methanol (10% solution w/v) was treated with 0.02 mol of potassium cyanide. After stirring under reflux during several hours (Table I), the reaction mixture was cooled and poured into water (200 ml). Extraction of the organic components was per-

formed with ether or dichloromethane (3x20 ml), the combined extracts were dried (magnesium sulphate) and, after removal of the drying agent, the solvent was evaporated to leave a clear oil. Normally the reaction mixtures were free of impurities (purity > 96%; checked by GLC and ^{1}H-NMR) and were not always distilled. If necessary compounds 4 could be further purified by preparative gas chromatography. The spectroscopic data of 2-cyanopiperidines 4 are compiled in Tables II and III.
Elemental analysis :

Compound 4a : Formula : $C_{11}H_{20}N_2$; Mol. weight : 180.29;
C (calcd) : 73.28%; C (found) : 73.40%;
H (calcd) : 11.18%; H (found) : 11.02%;
N (calcd) : 15.54%; N (found) : 15.70%.
Compound 4b : Formula : $C_{12}H_{22}N_2$; Mol. weight : 194.32;
C (calcd) : 74.17%; C (found) : 74.10%;
H (calcd) : 11.41%; H (found) : 11.20%;
N (calcd) : 14.42%; N (found) : 14.50%
Compound 4c : Formula : $C_{15}H_{20}N_2$; Mol. weight : 228.34;
C (calcd) : 78.90%; C (found) : 79.00%;
H (calcd) : 8.83%; H (found) : 8.80%;
N (calcd) : 12.27%; N (found) : 12.30%.

Reaction of δ-chloroimine 1e with potassium cyanide

The reaction of δ-chloroimine 1e (0.01 mol) with potassium cyanide (0.02 mol) in methanol (10% solution w/v) was performed in the same way as in the general procedure described above. After workup 2-cyanopiperidine 4e was isolated in 90% yield. By distillation or by isolation of compound 4e by preparative gas chromatography compound 4e was totally transformed into enamine 7 which was isolated as the sole product.

1-Isopropyl-2-phenyl-1,4,5,6-tetrahydropyridine 7

^{1}H-NMR (60 MHz, $CDCl_3$) : δ 0.94 (6H,d,J=6.4Hz,$CH(C\underline{H}_3)_2$); 0.80-2.40 (4H,m, $NC\underline{H}_2C\underline{H}_2$); 2.95-3.20 (2H,m,$C\underline{H}_2C$=); 3.40 (1H,septet,J=6.4Hz,$C\underline{H}(CH_3)_2$); 4.77 (1H,m,C$\underline{H}$=); 7.00-7.50 (5H,m,$C_6\underline{H}_5$).
IR (NaCl) $\nu_{C=C}$: 1628 cm^{-1}.
^{13}C-NMR (20 MHz, $CDCl_3$) : δ 146.8 and 141.0 (2xs,$\underline{C}$=CH and $\underline{C}$q); 127.9; 127.5 and 127.0 (3xd,$\underline{C}$o,$\underline{C}$m and $\underline{C}$p); 104.3 (d,C=$\underline{C}$H); 49.1 (d,$\underline{C}H(CH_3)_2$); 41.3 (t,$\underline{C}H_2$); 23.7 (t,$\underline{C}H_2$); 22.8 (t,$\underline{C}H_2$); 19.9 (q,$\underline{C}H_3$).
Mass Spectrum (70 eV) m/e (%) : 201(M^+,55); 200(26); 187(31); 186(100); 179 (35); 171(21); 158(25); 156(21); 155(21); 149(19); 143(15); 142(16); 140 (38); 135(38); 128(28); 127(40); 126(20); 117(30); 115(28); 114(16); 113

(20); 112(76); 105(32); 104(26); 103(14); 102(33); 99(49); 98(25); 97(19); 92(16); 91(24); 84(20); 83(24); 78(29); 71(28); 70(54); 69(35); 58(54); 57(68); 56(32); 55(47); 46(22); 45(22); 44(46); 43(28); 42(46); 41(64); 40(94); 39(40).

Elemental analysis :
Formula : $C_{14}H_{19}N$; Mol.weight : 201.31;
C (calcd) : 83.53%; C (found) : 83.50%;
H (calcd) : 9.51%; H (found) : 9.25%;
N (calcd) : 6.96%; N (found) : 6.80%.

Synthesis of piperidine 13

A solution of 0.01 mol of δ-chloroimine 1c in 20 ml of dry ether was treated with potassium tert-butoxide (0.02 mol) at reflux during three hours. Afterwards the reaction mixture was poured into 200 ml of water. The aqueous phase was extracted with dichloromethane (3x50 ml). The combined extracts were dried ($MgSO_4$), the drying agent was removed and the solvent was evaporated. The residual reaction mixture contained aldimine 12 as the sole compound. A solution of 0.01 mol of aldimine 12, prepared as described above, in dry methanol (10% solution w/v) was treated with 0.02 mol of potassium cyanide. After stirring under reflux during twenty hours, the reaction mixture was cooled and afterwards poured into water (200 ml). Extraction of the organic components was performed with dichloromethane (3x20 ml), the combined extracts were dried ($MgSO_4$) and after removal of the drying agent the solvent was evaporated to leave piperidine 13 of sufficient purity. Piperidine 13 could be isolated by preparative GLC (overall yield from 1c : 77%).
^{1}H-NMR (60 MHz, $CDCl_3$) : δ 0.91 (6H,s,$(C\underline{H}_3)_2$; 0.80-2.00 (4H,m,$(C\underline{H}_2)_2$); 2.13 (2H,s,$C\underline{H}_2N$); 2.20-2.60 (2H,t,J=5Hz,$C\underline{H}_2N$); 4.78 (1H,s,$C\underline{H}CN$); 7.00-7.60 (5H,m, $C_6\underline{H}_5$). IR (NaCl) $\nu_{C\equiv N}$: 2224 cm^{-1}.
^{13}C-NMR (20 MHz, $CDCl_3$) : δ 133.8 (s,$\underline{C}q$); 128.6; 128.5 and 127.6 (3xd,$\underline{C}o$,$\underline{C}m$ and $\underline{C}p$); 115.4 (s,$\underline{C}$ N); 62.8 (d,$\underline{C}H$); 61.9 (t,$\underline{C}H_2$); 50.9 (t,$\underline{C}H_2$); 37.2 (t,$\underline{C}H_2$); 31.0 (s,$\underline{C}(CH_3)_2$); 27.3 and 26.7 (2xq,$(\underline{C}H_3)_2C$); 22.2 (t,$\underline{C}H_2$).

Synthesis of piperidines 5 (General Procedure)

A solution of 0.01 mol of δ-chloroimine 1 in freshly distilled dry ether (10% w/v) was treated with 0.02 mol of lithium aluminium hydride. The reaction was stirred under reflux during several hours as indicated in Table I. Afterwards, the reaction mixture was poured into 200 ml of water and extracted with ether (3x30 ml). The combined extracts were dried ($MgSO_4$), the drying agent was removed and the solvent evaporated. The residue was

analyzed by ^{1}H-NMR and preparative gas chromatography, revealing only one compound (> 95%) i.e. piperidine 5, or was distilled. The spectral data of piperidines 5 are compiled in tables II and III.

Elemental analyses :

Compound 5a : Formula : $C_{10}H_{21}N$; Mol. Weight : 155.28;
C (calcd) : 77.35%; C (found) : 77.50%;
H (calcd) : 13.63%; H (found) : 13.60%;
N (calcd) : 9.02%; N (found) : 9.15%.

Compound 5b : Formula : $C_{11}H_{23}N$; Mol. Weight : 169.31;
C (calcd) : 78.04%; C (found) : 78.00%;
H (calcd) : 13.69%; H (found) : 13.75%
N (calcd) : 8.27%; N (found) : 8.30%.

Compound 5c : Formula : $C_{14}H_{21}N$; Mol. Weight : 203.33;
C (calcd) : 82.70%; C (found) : 82.60%;
H (calcd) : 10.41%; H (found) : 10.40%;
N (calcd) : 6.89%; N (found) : 6.90%.

Compound 5e : Formula : $C_{14}H_{21}N$; Mol. Weight : 203.33;
C (calcd) : 82.70%; C (found) : 82.55%;
H (calcd) : 10.41%; H (found) : 10.50%;
N (calcd) : 6.89%; N (found) : 6.95%.

Reaction of δ-chloroimine 1d with lithium aluminium hydride in ether

The reaction of δ-chloroimine 1d with lithium aluminium hydride in ether was performed as described above. If the reaction was performed at room temperature (Table I, entry 9) only amine 17d could be isolated while if the reaction was performed at reflux temperature only piperidine 5d was isolated.

N-t-Butyl-N-(5-chloro-2-methyl)pentylamine 17d

^{1}H-NMR (60 MHz, $CDCl_3$) : δ 1.09 (9H,s,C(CH_3)$_3$); 0.60-3.20 (10H,m,-(CH_2)$_2$-$CH(CH_3)$-CH_2-); 3.51 (2H,t,J=6Hz,CH_2Cl).

Reaction of δ-chloroimine 1e with lithium aluminium hydride in ether

The reaction of δ-chloroimine 1e with lithium aluminium hydride in ether was performed in the same way as described above. In the residue, next to piperidine 5e, also amine 17e was present (30%) which was isolated from the reaction mixture by crystallisation (17e : mp. 130°C).

N-Isopropyl-N-(5-chloro-1-phenyl)pentylamine 17e

^{1}H-NMR (60 MHz, $CDCl_3$) : δ 0.98 and 1.17 (6H,2xd,J=6.4Hz,CH(CH_3)$_2$); 0.80-

3.20 (7H,m,-($C\underline{H}_2$)$_3$- and $C\underline{H}(CH_3)_2$); 3.46 (2H,t,J=6.2Hz,$C\underline{H}_2Cl$); 4.00-4.50 (1H,m,$C\underline{H}$); 7.30-8.00 (5H,m,$C_6\underline{H}_5$).

^{13}C-NMR (20 MHz, $CDCl_3$) : δ 134.2 (s,$\underline{C}q$); 129.5; 129.4; 128.4 (3xd,$\underline{C}o$,$\underline{C}m$ and $\underline{C}p$); 60.8 (d,$\underline{C}H$); 48.2 (d,$\underline{C}H$); 44.3 (t,$\underline{C}H_2Cl$); 33.5; 32.0 and 23.4 (3xt,-($\underline{C}H_2$)$_3$-); 20.6 and 17.7 (2xq,CH($\underline{C}H_3$)$_2$).

IR (KBr) : ν_{NH} = 3420 cm^{-1}.

Mass Spectrum : no M^+; 187(9); 186(10); 172(19); 135(10); 128(10); 127(54); 119(27); 118(21); 113(7); 112(25); 102(19); 97(15); 95(7); 91(22); 84(15); 83(7); 72(25); 71(25); 70(18); 69(25); 65(7); 59(27); 58(54); 57(100); 56(27); 55(54); 53(7); 46(34); 45(13); 44(28); 43(88); 42(27); 41(66); 40(45); 39(19).

Preparation of 2-alkoxypiperidines 6 (General Procedure)

The preparation of 2-alkoxypiperidines 6 (0.01 mol) was performed by reaction of δ-chloro imines 1 with methanol (10% solution w/v), with sodium methoxide in methanol (2 molar equivalents of a 2N solution), with potassium thiocyanate in methanol (KSCN : 2 molar equivalents; MeOH : 10% solution w/v) or with sodium isopropoxide in isopropanol (2 molar equivalents of a 2N solution). The reaction mixture was refluxed during several hours (Table I) and afterwards poured into 200 ml water. The aqueous phase was extracted with dichloromethane (3x50 ml). The combined extracts were dried ($MgSO_4$), the drying agent was removed and the solvent was evaporated leaving 2-alkoxypiperidines 6 in high yield (purity >, 95%). The spectral data of 2-alkoxypiperidines 6 are compiled in Tables II and III.

Elemental analyses :

Compound 6a : Formula : $C_{11}H_{23}NO$; Mol. Weight : 185.31;
C (calcd) : 71.30%; C (found) : 71.20%;
H (calcd) : 12.51%; H (found) : 12.40%;
N (calcd) : 7.56%; N (found) : 7.60%.

Compound 6b : Formula : $C_{12}H_{25}NO$; Mol. Weight : 199.34;
C (calcd) : 72.31%; C (found) : 72.40%;
H (calcd) : 12.64%; H (found) : 12.70%;
N (calcd) : 7.03%; N (found) : 7.10%.

The transformation of 2-methoxypiperidine 6a into piperidine 5a

The transformation of 2-methoxypiperidine 6a into piperidine 5a was performed in the same way as described for the synthesis of piperidines 5. Via this procedure piperidine 5a could be prepared in 95% yield (^{1}H-NMR, GLC, GC-MS). The spectral data of piperidine 5a are compiled in Tables II

and III.

References

£ Present address : "Laboratory of DSM Chemicals b.v." DSM Limburg b.v., 6160 MB GELEEN, The Netherlands.

* N. De Kimpe, to whom correspondence should be addressed, "Senior Research Associate" (Onderzoeksleider) of the Belgian "National Fund for Scientific Research" (Nationaal Fonds voor Wetenschappelijk Onderzoek).

1. Dagonneau, M.; Kagan, E.S.; Mikhailov, V.I.; Rozantsev, E.G.; Sholle, V.D. Synthesis, 1984, 895-916.
2. Fodor, G.B.; Colasanti, B. Alkaloids, Chem. Biol. Perspect., 1985, 3, 1-90.
3. Hunt, J.D.; McKillop, A. Rodd's Chem. Carbon Compd (2nd Ed.), 1978, Volume 4, Issue G, 115-169, Ed. Coffey, S. and Ansell, M.F., Elsevier Amsterdam.
4. Gross, D. Fortschritte Chem. Org. Naturst., 1971, 29, 1-59.
5. Stunz, G.M.; Findlay, J.A. Alkaloids (Academic Press), 1985, 26, 89-183.
6. Encyclopedia of Plant Physiology, New Series, 1980, Vol. 8 (Secondary Plant Products) Eds. Bell E.A. and Charlwood B.V., Springer Verlag.
7. The Biochemistry of Plants "A Comprehensive Treatise" Stumpf P.K. and Conn E.E., 1981, Vol. 7 (Secondary Plant Products) Ed. Conn E.E., Academic Press.
8. Gilbertson, T.J. Phytochemistry, 1972, 11, 1737.
9. Gupta, R.N.and Spenser, I.D. Phytochemistry, 1969, 8, 1937.
10. Leistner, E.; Gupta, R.N. and Spenser, I.D. J. Am. Chem. Soc., 1973, 95, 4040.
11. Keogh, M.F. and O'Donovan, D.G. J. Chem. Soc. (C), 1970, 1792.
12. Gupta, R.N. and Spenser, I.D. Phytochemistry, 1970, 9, 2329.
13. O'Donovan, D.G. and Creedon, P.B. Tetrahedron Lett., 1971, 1341.
14. Keogh, M.F. and O'Donovan, D.G. J. Chem. Soc. (C), 1970, 2470.
15. Sulmon, P.; De Kimpe, N. and Schamp, N. Synthesis, 1989, 8.
16. Sulmon, P.; De Kimpe, N.; Verhé, R.; De Buyck, L. and Schamp, N. Synthesis, 1986, 192.
17. Sulmon, P.; De Kimpe, N. and Schamp, N. Tetrahedron, 1988, 44, 3653.
18. Sulmon, P.; De Kimpe, N. and Schamp, N. Tetrahedron (in press).
19. Evans, D.A. J. Am. Chem. Soc., 1970, 92, 7593-7595.
20. Kikumoto, R.; Ito, M. and Nakamura, A. Japan. Kokai, 1973 73, 76,877 (Cl.16E431.1), 16 Oct., Appl. 1972, 72 07,792, 20 Jan., Chem. Abstr. 1974, 80, 37004g.

21. Guerrier, L.; Royer, J.; Grierson, D.S. and Husson, H.-P. J. Am. Chem. Soc., 1983, 105, 7754.
22. Royer, J. and Husson, H.-P. Tetrahedron Lett., 1985, 1515.
23. Royer, J. and Husson, H.-P. J. Org. Chem., 1985, 50, 670.
24. Osdene, T.S. and Sanders, E.B., U.S. Patent, 1978 4,093,620 (Cl. 260-291, C07D213/57), 6 Jun., Appl. 1976, 694,687, 10 Jun.; Chem. Abstr., 1978 89, 594.
25. Gless, R.D. and Rappoport, H. J. Org. Chem., 1979, 44, 1324.
26. Grierson, D.S.; Harris, M. and Husson, H.-P. J. Am. Chem. Soc., 1980, 102, 1064.
27. Ward, D.P.; Trevor, A.J.; Kalir, A.; Adams, J.D.; Baillie, T.A. and Castagnoli Jr., N. Drug. Metab. Dispos., 1982, 10, 690.
28. Hoag, M.K.P.; Trevor, A.J.; Asscher, Y.; Weissman, J. and Castagnoli Jr., N. Drug. Metab. Dispos., 1984, 12, 371.
29. Kalier, A.; Trevor, A.J.; Ward, D.P.; Adams, J.D.; Baillie, T. and Castagnoli, N. Chem. Abstr., 1985, 102, 125007p.
30. Chiba, T. and Takato, Y. J. Org. Chem., 1977, 42, 2973.
31. Duquet, D.; Callens, R.E.A.; Borremans, F.A.M. and Anteunis, M.J.O. Bull. Soc. Chim. Belg., 1981, 51.
32. Takahashi, K.; Iida, H. and Nishino, H. Jpn. Kokai Tokkyo Koho 1985 JP 60,190,762 (85,190,762) (Cl. C07D211/60), 28 Sep., Appl. 84/46,160, 9 Mar. 1974, Chem. Abstr., 1986 104, 109489h.
33. Takahashi, K.; Kurita, H.; Ogura, K. and Iida, H. J. Org. Chem., 1985, 50, 4368.
34. Takahashi, K.; Mikajiri, T.; Kurita, H.; Ogura, K. and Iida, H. J. Org. Chem., 1985, 50, 4372.
35. Kikumoto, R.; Ito, M.; Nakamura, A. and Nomura, T. Ger. Offen. 1973, 2,256,771 (Cl.C07c), 24 May, Japan Appl. 1971, 71 92,838, 19 Nov., Chem. Abstr., 1973, 79, 42844g.
36. Kikumoto, R.; Ito, M.; Nakamura, A. and Nomura, T. Japan Kokai 1973, 73 56,677 (Cl. 16E362.1), 9 Aug., Appl. 1971, 71 92,839, 19 Nov., Chem. Abstr. 1974, 80, 37112r.
37. Kikumoto, R.; Ito, M. and Nomura, T. Japan. Kokai, 1973, 73 96,589 (Cl.16E362.1), 10 Dec., Appl. 1972, 72 14,551, 10 Feb., Chem. Abstr. 1974, 80, 416.
38. Kikumoto, R.; Ito, M. and Nomura, T. Japan. Kokai, 1973, 73 96,516 (Cl.16B651), 10 Dec., Appl. 1972, 72 14,550, 10 Feb., Chem. Abstr. 1974, 80, 96359z.
39. Barton, D.H.R.; Billion, A. and Boivin, J. Tetrahedron Lett., 1985, 1229.

40. Unkovskii, B.V.; Romanova, K.I.; Sokolova, T.D.; Bogatkov, S.V. and Malina, Yu.F. Khim. Geterosikl. Soedin. 1976, 89; Chem. Abstr. 1976, 84, 163948p.
41. Romanova, K.I.; Sokolova, T.D.; Malina, Yu.F. and Unkovskii, B.V. Izv. Vyssh. Ucheln. Zaved., Khim. Khim. Tekhnol., 1976, 19, 563; Chem. Abstr. 1976, 85, 62920p.
42. Chasnikova, S.S.; Sokolova, T.D.; Mironova, N.A.; Artyukhin, V.I.; Malina, Yu.F.; Agashkin, O.V. and Unkovskii, B.V. Chem. Abstr. 1976, 87, 52626z.
43. Mitzlaff, M.; Warning, K. and Jensen, H. Justus Liebigs Ann. Chem., 1978, 1713.
44. Eberson, L.; Hlavaty, J.; Jonsson, L.; Nyberg, K.; Servin, R.; Sternerup, H. and Wistrand, L.G. Acta Chem. Scand., Ser. B., 1979, B 33, 113.
45. Warning, K. and Mitzlaff, M., Tetrahedron Lett., 1979, 1565.
46. Palasz, P.D.; Utley, J.H.P. and Hardstone, J.D. J. Chem. Soc. Perkin Trans. II, 1984, 807.
47. Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K.; Kanazawa, T. and Tsuda, K. J. Org. Chem., 1984, 49, 3711.
48. Palasz, P.D.; Utley, J.H.P. and Hardstone, J.D. Acta Chem. Scand., Ser B, 1984, B 38, 281.
49. Duquet, D.; Callens, R.E.A.; Anteunis, M.J.O. and Borremans, F.A.M. Bull. Soc. Chim. Belg., 1984, 93, 927.
50. Schöpf, C.; Koop, H. and Werner, G., Chem. Ber., 1960, 93, 2457.
51. Wiessler, M. Angew. Chem., 1974, 86, 817.
52. Warning, K. and Mitzlaff, M. Ger. Offen. 1978, 2,636,098 (Cl.C07D521/00), 16 Feb.; Appl. 1976, 11 Aug.; Chem. Abstr. 1978, 88, 152670y.
53. Mueller, E.; Kettler, R. and Wiessler, M. Justus Liebigs Ann. Chem., 1984, 1468.