Tetrahedron Vol. 38, No. 3, pp. 413 to 417, 1982
Printed in Great Britain.

0040-4020/82/030413-05$03.00/0

ENAMINE CHEMISTRY—XXV†

REDUCTION OF ENAMINONES BY $LiAlH_4$ AND $NaBH_4$. SYNTHESIS OF α,β-UNSATURATED ALDEHYDES

S. CARLSSON and S.-O. LAWESSON
Department of Organic Chemistry, University of Aarhus, DK-8000 Aarhus C, Denmark

(*Received in UK 2 June* 1981)

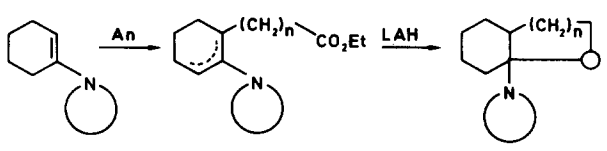
Abstract—Cyclohexanone, 2-methyl-cyclohexanone and 4-methyl-cyclohexanone, **1**, were transformed into the enaminones **4a–4e** by the following two routes: (A): Acylation of the enamines, **2**, derived from **1** and secondary amines (pyrrolidine, morpholine and piperidine) by ethyl chloroformate, and (B): Condensation of **1** with diethyl oxalate, giving the β-ketoesters **3**, followed by reaction with the secondary amines. Ethyl 2(-1-pyrrolidinyl)-1-cyclopentene-1-carboxylate, **4f**, and methyl 3-(1-pyrrolidinyl)-2-butenoate, **4g**, were prepared from ethyl 2-oxo-1-cyclopentanecarboxylate and ethyl 3-oxo-butanoate, respectively, by condensation with pyrrolidine. Reduction of **4a** by LAH afforded 1-cyclohexen-1-carboxaldehyde, **5a**, 1-cyclohexene-1-methanol, **6a**, and 1-(1-cyclohexene-1-methyl)pyrrolidine, **7a**, in yields depending on the molar ratio of LAH/**4a**. Reduction of **4f** by LAH gave cyclopenten-1-methanol, **6b**, 1-(1-cyclopentene-1-methyl)pyrrolidine, **7b**, and ethyl-2(1-pyrrolidinyl)-1-cyclopentanecarboxylate, **8b**. Compound **4g**, when reduced with LAH, yielded methyl 3-(1-pyrrolidinyl) butanoate, **8c** (main product) and 1-(2-butenyl)pyrrolidine, **7c** (minor). Reduction of **4** by $NaBH_4$ afforded exclusively the saturated β-aminoesters, **8**, in high yields. The reductions with LAH and $NaBH_4$ are rationalized in terms of the HSAB principle.

We have for some time been interested in reductive cyclization of enamines and new syntheses of condensed furan and pyran derivatives.[1,2] Lithium aluminium hydride attacks exclusively the ester group in the alkylated enamines ($n = 1, 2$) giving by subsequent cyclization the furan and pyran derivatives. The orientation of the double bond in these enamino esters is mainly to the least substituted carbon (C2–C3). By shortening the length of the ester side chain (n = 0), the orientation of the double bond changes to the most substituted carbon (C1–C2), owing to the introduced conjugation between the ester group and the enamine function. The chemical properties are thereby changed. Enaminones[3] are known to exhibit ambident reactivity towards electrophiles[4] as well as nucleophiles.[5–8] This publication reports on synthesis and reduction of vinylogous urethanes.

The enaminones **4a–4e** were prepared by the following two routes (Scheme 2): Cyclohexanone, 2-methyl-cyclohexanone and 4-methyl-cyclohexanone, **1**, were reacted with secondary amines (pyrrolidine, morpholine and piperidine) to give the enamines **2**.[9] Acylation of **2** gave only traces of **4**. By using two moles of the enamines, **2** (one mole as a base instead of Et_3N) the yields of **4** were increased to 14–24%. The low yields of the desired products, **4**, can, however, be accounted for by the HSAB principle.[10] The chloroformate C is classified as a hard acid and the β-C as a soft base. The main reaction is expected to be acylation on N (a hard base) to give the unstable enammonium salts, **4**, which when heated are transformed back into **2**. By the second route (B), the cyclohexanones **1** were condensed with diethyoxalate giving, after elimination of CO, the β-keto esters **3**.[11] Subsequent reaction with secondary amines resulted in high yields of the enaminones **4** (the total yield of **4** from the starting ketones **1** being 49–57% by route B).

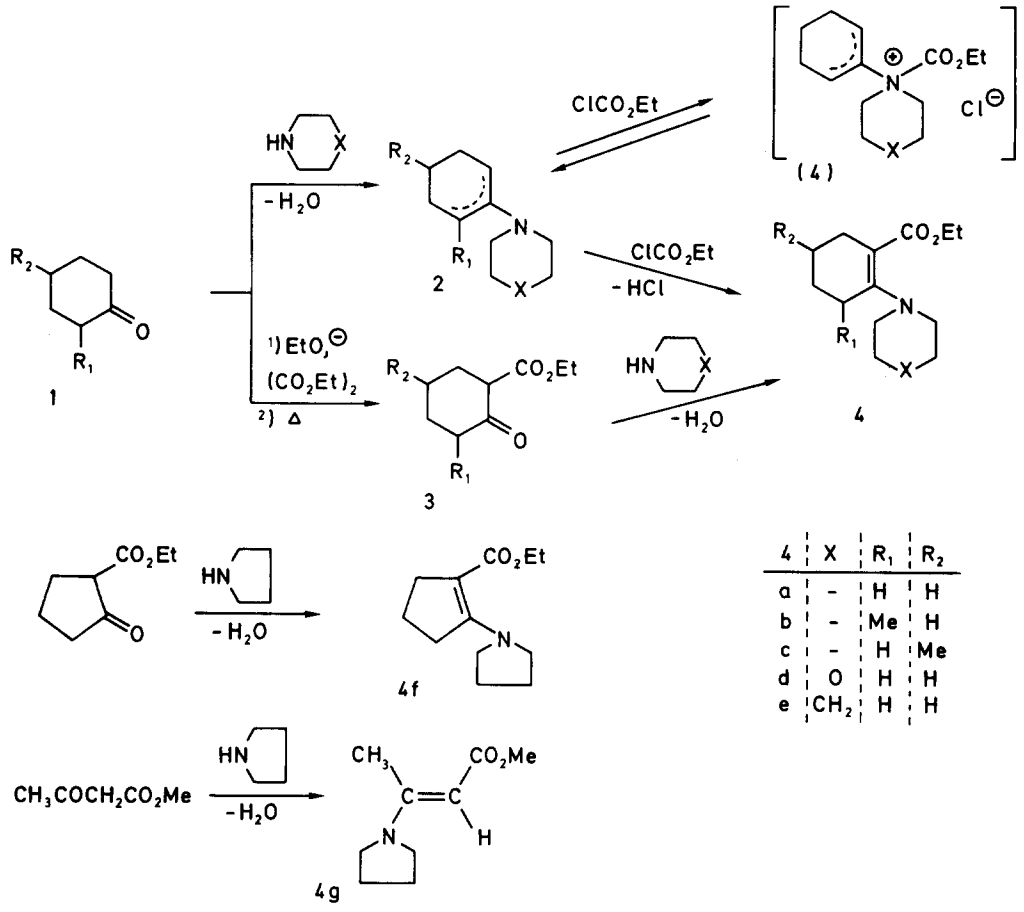
Ethyl 2 - (1 - pyrrolidinyl) - 1 - cyclopentene - 1 - carboxylate, **4f**, and methyl 3-(1-pyrrolidinyl)-2-butenoate, **4g**, were prepared from ethyl 2-oxo-1-cyclopentanecarboxylate (easily obtained from ethyl adipate by Dickmann condensation[12]) and methyl acetoacetate, respectively, by condensation with pyrrolidine. The enaminones **4a–4g** were characterised by IR, MS, ^1H NMR, ^{13}C NMR (Table 1) and by comparison with authentic materials.[13] The carbon resonances of the vinyllic carbons could easily be identified using the additivity rules.[14] Compared with simple enamines[15] the resonances of the β-carbons (to the ester group) are shifted downfield (δ(C=C–COOR) = 155–169 ppm), and the α-carbons are shifted to higher field (δ(C=C–COOR) = 83–97 ppm). All compounds **4** show IR ab-

†Part XXIV. A. A. El-Barbary, S. Carlsson and S.-O. Lawesson, *Tetrahedron* **38**, 405 (1982).



A_1: $BrCH_2CO_2Et$, A_2: $CH_2=CHCO_2Et$

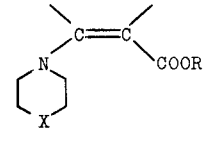
Scheme 1.



4	X	R_1	R_2
a	-	H	H
b	-	Me	H
c	-	H	Me
d	O	H	H
e	CH_2	H	H

Scheme 2.

Table 1. Yield and physical data of 4



4

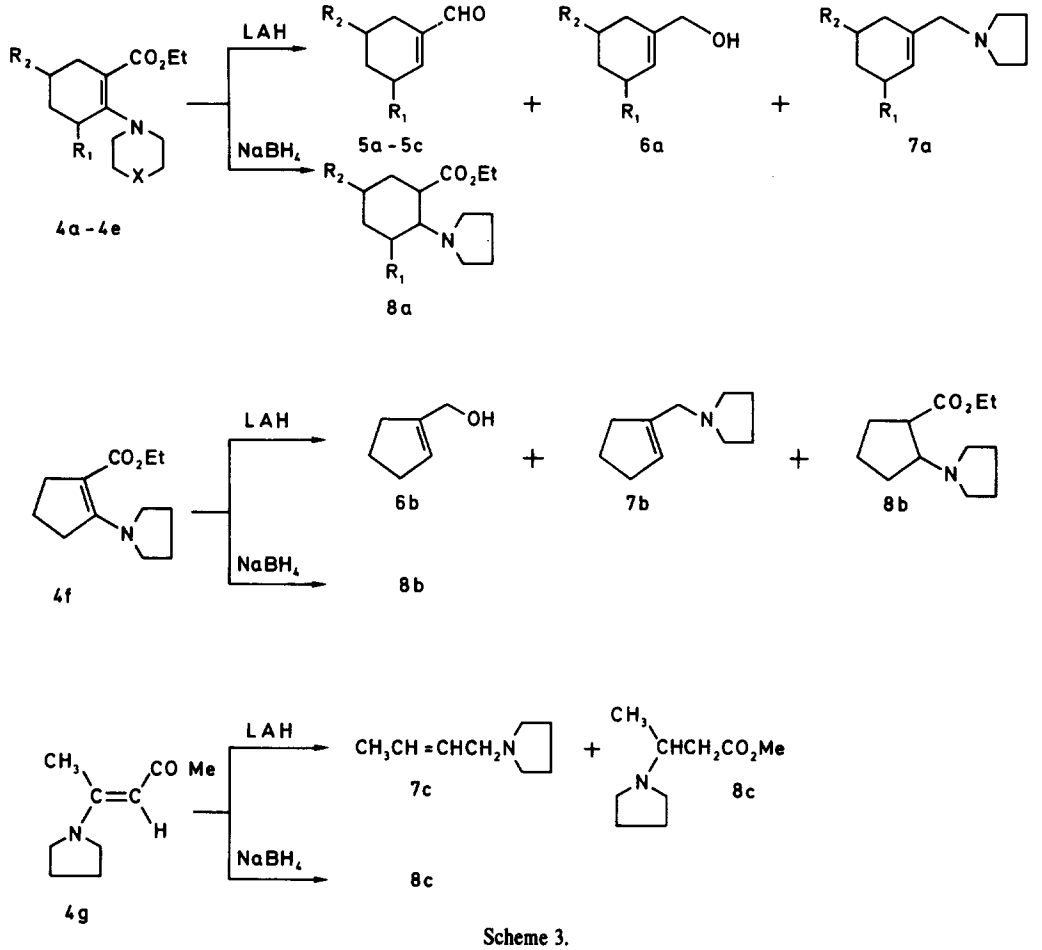
4	B.p.(°C/torr)	Yield (%) from 1 by route A	Yield (%) from 1 by route B	^{13}C NMR (δ ppm) C=O	C=C-N	C=C-N	CH_2N	CH_2X	other carbons
a	112/0.4	24	49	167.4	155.0	93.5	50.7	25.3	58.3(OEt), 30.5, 27.0, 22.7(2 C), 14.4(OEt).
b	110/0.3		51	167.4	154.9	93.0	50.7	25.2	58.4(OEt), 36.2, 30.9, 30.0, 28.9, 21.9, 14.4(OEt).
c	120/0.4		54	167.5	154.8	93.1	50.9	25.3	58.4(OEt), 35.8, 30.7, 30.5, 28.8, 21.3, 14.5(OEt).
d	122/0.3	14	51	166.8	161.5	94.9	51.0	67.1	57.8(OEt), 34.9, 31.9, 24.0, 19.9, 14.2(OEt).
e	116/0.25	18	50	171.6	168.3	97.0	47.9	26.6	58.0(OEt), 29.6, 26.3, 22.1(2 C), 21.6, 14.0(OEt).
f	110/0.35		57	166.1	159.2	93.8	51.8	25.7	58.5(OEt), 46.5, 32.8, 21.1, 14.8(OEt).
g	M.p. 69°C		93*	169.1	159.2	82.7	47.6	24.8	49.3(OMe), 16.2(CH_3).

* From methyl acetoacetate.

sorptions at 1660–70 cm^{-1} (C=O) and 1580–90 cm^{-1} (C=C). The CO absorption is lowered about 60 cm^{-1} compared to simple unsaturated esters.[16]

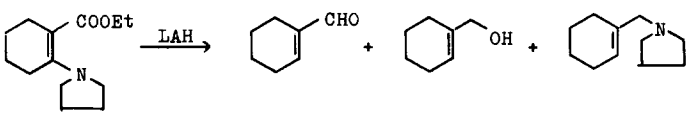
Reduction of the enaminones **4**. When ethyl 2 - (1 - pyrrolidinyl) - 1 - cyclohexene - 1 - carboxylate **4a** was reacted with LAH, 1 - cyclohexen - 1 - carboxaldehyde, **5a**, 1 - cyclohexen - 1 - methanol, **6a**, and 1 - (1 - cyclohexenmethyl)pyrrolidine, **7a**, were isolated in variable yields, depending on the amount of the reducing agent (Scheme 3 and Table 2).

While the allylic alcohol, **6a**,[17,18] and ethyl 2-oxo-1-cyclohexanecarboxylate[19] have been reported, the formation of the unsaturated aldehyde, **5a**, and the allylic amine, **7a**, were quite unexpected. The mechanism for the formation of compounds **5a–7a** is not clear. The reduction may proceed through a 1,4 addition–elimination giving ethyl 1-cyclohexene-1-carboxylate, **9**, together with the pyrrolidine salt, **10**. Further reduction of **9** by $H^{\ominus}$ leads to **6a**, while attack on **9** by the hard base, **10**, gives the enamide **11** (A similar result has been reported



Scheme 3.

Table 2.



LAH/4a	Yield[a] (%)		
0.5[b]	21	5	8
1.0	56	9	25
2.0	21	45	25

[a] Determined by GLC.

[b] Recovered 4a : 46%.

from the reaction between piperidinocrotonates and Grignard reagents[7]). Reduction of the tertiary amide, **11**, to give the aldehyde **5a**, and the amine, **7a**, is in agreement with the literature.[20]

The structure of the compounds **5a–7a** was elucidated by IR, MS, ^{1}H NMR, ^{13}C NMR and by comparison with authentic materials[18,19,21] (**5a, 7a**). In the ^{13}C NMR spectrum of **7a** the vinylic carbons exhibit resonances at 135.6 ppm (C1) and 123.8 ppm (C2) (in reasonable agreement with the calculated[14] values 137.2 (C1) and 126.0 (C2), respectively). The allylic carbon α to pyrrolidine is found at 63.5 ppm. In the ^{1}H NMR spectrum of **7a** the allylic hydrogens (C=C–CH_2–N⟨) show a singlet at 2.9 ppm. The mass spectrum of **7a** shows intense absorptions at 165 ($M^{\oplus}$), 84 (⟨N–$CH_2^{\oplus}$) and 70 (⟨$N^{\oplus}$).

α,β-Unsaturated aldehydes are important compounds and 1-cyclohexen-1-carboxaldehyde (and the 4-substituted ones) have found industrial uses[22,23] and have been studied in reactions with organometallic compounds.[24,25]

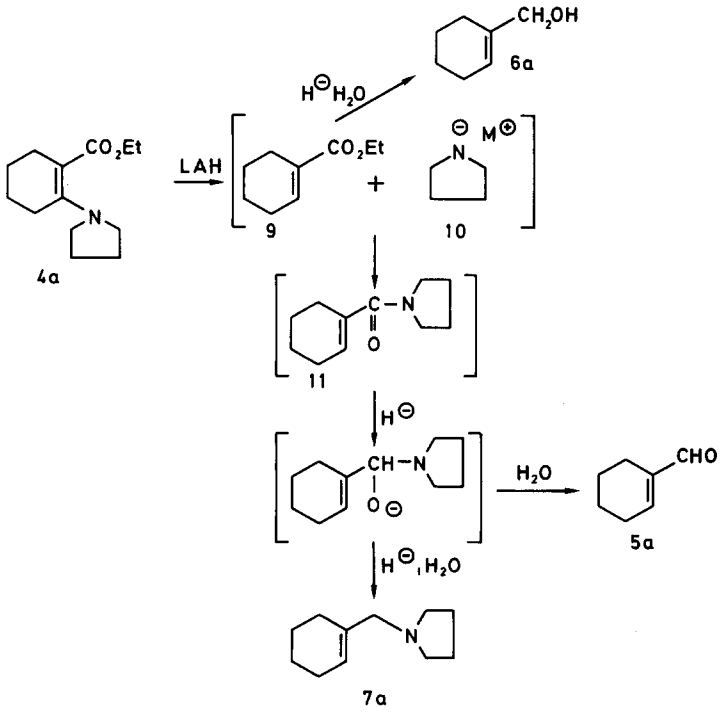
Attempts were therefore made to optimize the yield of **5a** (Table 2), and it was found that using equimolar amounts of reducing agent and substrate quite good yields of the unsaturated aldehyde could be obtained. Under these conditions the enaminones **4b–4g** were reduced. Compounds **4b** and **4c** (ethyl 3 - methyl - 2(1 - pyrrolidinyl) - cyclohexene - 1 - carboxylate and ethyl 5 - methyl - 2(1 - pyrrolicinyl) - 1 - cyclohexene - 1 - carboxylate) afforded the corresponding unsaturated aldehydes, **5b** and **5c**, in similar yields. By changing the secondary amine in compound **4a** to morpholine, **4d**, and piperidine, **4e**, the yield of **5a** was decreased to 15% and 17%, respectively. When ethyl 2 - (1 - pyrrolidinyl) - 1 - cyclopentene - 1 - carboxylate, **4f**, was reduced under the same conditions, ethyl 2(1 - pyrrolidinyl) - 1 - cyclopentanecarboxylate, **8b**, 1-cyclopenten-1-methanol, **6b**, and 1 - (1 - cyclopentene - 1 - methyl) - pyrrolidine, **7b**, were isolated (no traces of 1-cyclopenten-1-carboxaldehyde were detected). Reduction of methyl 3 - (1 - pyrrolidinyl) - 2 - butenoate, **4g**, by LAH afforded as main product the saturated β-aminoester, methyl - 3(1 - pyrrolidinyl) - 2 - butanoate, **8c**, together with a small amount of the allylic amine, 1-(2-butenyl)pyrrolidine, **7c**. The β-amino esters **8b** and **8c** were formed by 1,4 reduction of the enaminone system.[6]

When $NaBH_4$, a mild reducing agent, was used instead of LAH, the β-aminoesters **8a–8c** were isolated as the only products in high yields. This is in agreement with the HSAB principle,[26] $NaBH_4$ is regarded as a soft base and the vinylic β-carbon as a soft acid (compared with the C=O-carbon), and with earlier reports on $NaBH_4$ reduction of enaminones.[5]

By metalhydride reduction of the easily prepared vinologous urethanes, **4**, an alternative route to α,β-unsaturated aldehydes, allylic alcohols, allylic amines and β-amino esters is at hand. The LAH reduction seems, however, to be sensitive to the stereochemistry of the enaminone—the aldehyde formation of the investigated substrates being restricted to cyclohexane derivatives.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer ($CDCl_3$) and the ^{13}C NMR spectra at 20 MHz on a CFT 20 Varian instrument ($CDCl_3$). TMS was used as internal standard. Chemical shifts are expressed in δ-values. IR spectra were recorded on a Beckman IR 18A spectrometer. Mass spectra and precise measurements were recorded on a Micromass 7070 mass spectrometer operating at 70 eV using direct inlet. Glc analyses were carried out on a Hewlett Packard 5700A gas



Scheme 4.

chromatograph equipped with a flame ionisation detector, using a 2m SE 30 DMCS glass column. Silica gel 60 (Merck) and Aluminium Oxide 60G (Merck) were used for column chromatography. M.ps and b.ps are uncorrected.

Starting materials. Compounds **2** and **3** were prepared by known methods[9,11,12] and enaminones **4a–4g** were prepared by route A according to lit.[9]

Enaminone formation by route B (**3→4**). Compound **3** (0.05 mole) and the secondary amine (0.05 mole) together with a catalytic amount of pTsOH were dissolved in 100 ml benzene or toluene and refluxed for 4 hr using a Dean–Stark apparatus for water separation. The solvent was evaporated and the enaminones were purified by distillation under reduced pressure (**4a–4g**) or by crystallisation from benzene–pentane (**4g**). Yields and spectral data are summarized in Table 1.

General procedure for reduction of the enaminones **4** *by* LAH (**4→5+6+7+8**). To an ice-cooled soln of LAH (0.02 mole) in anhyd ether (50 ml, stirring, N_2) compound **4** (0.02 mole) was added dropwise (5 min). Stirring was continued at room temp for 2 hr. Then at 0°, 7 g 3% NaOH was added dropwise (10 min). The icebath was removed and stirring continued for 15 min at room temp. The mixture was filtered and extracted twice with ether. The combined ether extracts were dried ($MgSO_4$), concentrated and the products **5–8** separated on a column (Al_2O_3 or SiO_2, ether–pentane).

General procedure for reduction of **4** *by* $NaBH_4$ (**4→8**). To an ice-cooled, stirred soln of $NaBH_4$ (0.06 mole) in 50 ml EtOH (for ethyl esters) or MeOH (for methyl esters) **4** (0.02 mole) was added. Stirring is continued at room temp for 16 hr. The mixture was decomposed by adding 20 ml 1% NaOH aq. Extraction and purification as above. Compound **5a** (yields Table 2); ^{13}C NMR (δ): 194.2 (CO), 151.4 (Ç=C–CHO), 141.6 (C=Ç–CHO), 26.5, 22.1, 21.8 (2C). ^1H NMR (δ): 9.55 (s, 1 H, CHO), 6.75 (s, 1 H, H–C=C), 2.2–2.4 (m, 4 H), 1.5–1.7 (m, 4 H). Compound **5b**, yield 51%; ^{13}C NMR (δ): 194.4 (CO), 156.4 (Ç=C–CHO), 140.5 (C=Ç–CHO), 31.4, 30.5, 21.1, 20.1 (2C). ^1H NMR (δ): 9.46 (s, 1 H, CHO), 6.65 (s, 1 H, H–C=C), 1.4–2.3 (m, 7 H), 1.16 (d, J = 7 Hz, 3 H, CH_3CH). IR (film, cm^{-1}): 1680 (s), 1640 (m). Compound **5c**, yield 41%; ^{13}C NMR (δ): 193.6 (CO), 150.6 (Ç=C–CHO), 141.0 (C=Ç–CHO), 29.9, 29.2, 27.3, 26.1, 21.1. ^1H NMR (δ): 9.48 (s, 1 H, CHO), 6.82 (t, J = 3 Hz, 1 H, H–C=C), 2.3–2.7 (m, 4 H), 1.3–1.9 (m, 3 H), 1.1 (d, J = 5 Hz, 3 H, CH_3CH). IR (film, cm^{-1}): 1680 (s), 1640 (m). Ms (rel. int. %): 124 (M^+, 71), 109 (47), 95 (100), 81 (34), 67 (36), 55 (35), 44 (61). Compound **6a** (yield Table 2). Physical data in agreement with authentic material.[18,19] Compound **6b**, yield 40%. Physical data in agreement with literature.[19] Compound **7a** (yield Table 2); ^{13}C NMR (δ): 135.6 (C1), 123.8 (C2), 63.5 (C=C–CH_2–N), 53.8 (CH_2N), 27.2, 25.0, 23.2 (ÇH_2CH_2N), 22.7, 22.3. ^1H NMR (δ): 5.58 (s, 1 H, H–C=C), 2.90 (s, 2 H, CH_2N), 2.45 (t, J = 6 Hz, 4 H, CH_2N), 1.5–2.2 (m, 12 H). Ms (rel. int. %): 165 (M^+, 99), 136 (26), 122 (11), 111 (37), 98 (17), 95 (28), 84 (100), 70 (93). Precise measurement on *m/e* = 165 (Calc. for $C_{11}H_{19}N$: 165.1517. Found: 165.1519). Compound **7b**, yield 19%; ^1H NMR (δ): 5.6 (t, J = 2.5 Hz, 1 H, H–C=C), 3.15 (s, 2 H, CH_2N), 2.30 (t, J = 6 Hz, CH_2N). Ms (rel. int. %): 151 (M^+, 67), 123 (32), 110 (23), 95 (18), 84 (15), 70 (100), 56 (36). Compound **7c**, yield 12%. Physical data in agreement with earlier reports.[27] Compound **8a**, yield 84% ($NaBH_4$); ^1H NMR (δ): 4.17 (q, J = 7 Hz, 2 H, OEt), 2.3–2.8 (m, 6 H), 1.25 (t, J = 7 Hz, 3 H, OEt). Ms (rel. int. %): 225 (M^+, 22), 182 (7), 180 (18), 152 (5), 124 (6), 110 (100), 98 (23), 70 (15). Precise measurement on *m/e* = 225 (Calc. for $C_{13}H_{23}NO_2$: 225.1728. Found: 225.1729). Compound **8b**, yield 31% (LAH), 78% ($NaBH_4$); ^1H NMR (δ): 4.20 (q, J = 7 Hz, 2 H, OEt), 2.30–2.85 (m, 6 H), 1.6–2.2 (m, 10 H), 1.15 (t, J = 7 Hz, 3 H, OEt). Ms (rel. int. %): 211 (M^+, 68), 182 (6), 170 (12), 166 (15), 110 (100), 96 (37), 84 (12), 70 (8), 67 (41). Precise measurement on *m/e* = 225 (Calc. for $C_{12}H_{21}NO_2$: 211.1571. Found: 211.1572). Compound **8c**, yield 63% (LAH), 81% ($NaBH_4$), b.p. 110°/12; ^1H NMR (δ): 3.70 (s, 3 H, OCH_3), 2.3–2.9 (m, 7 H), 1.8 (m, 4 H), 1.12 (d, J = 5 Hz, 3 H, CH_3CH). Ms (rel. int. %): 171 (M^+, 6), 156 (37), 136 (6), 124 (12), 110 (9), 98 (100), 84 (13), 70 (24), 56 (26). Precise measurement on *m/e* = 171 (Calc. for $C_9H_{17}NO_2$: 171.1258. Found: 171.1258).

REFERENCES

[1] S. Carlsson and S.-O. Lawesson, *Tetrahedron* **36**, 3585 (1980).
[2] S. Carlsson, A. A. El-Barbary and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **89**, 643 (1980).
[3] J. V. Greenhill, *Chem. Soc. Rev.* **6**, 277 (1977).
[4] R. Shabana, J. B. Rasmussen and S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **90**, 75 (1981).
[5] L. Nilsson, *Acta Chem. Scand.* **B33**, 547 (1979).
[6] G. N. Walker, *J. Org. Chem.* **27**, 4227 (1962).
[7] G. Schroll, H. J. Jakobsen and S.-O. Lawesson, *Recl. Trav. Chim. Pays-Bas* **84**, 597 (1965).
[8] P. Slosse and C. Hootele, *Tetrahedron Letters* 4587 (1979).
[9] G. Stork, A. Brizzolara, H. Landesmans, J. Szmuszkovicz and R. Terrell, *J. Am. Chem. Soc.* **85**, 207 (1963).
[10] T-L. Ho, *Hard and Soft Acids and Bases Principle in Organic Chemistry*, p. 43. Academic Press, New York (1977).
[11] H. R. Snyder, L. A. Brooks and S. H. Shapiro, *Org. Syntheses* Coll. Vol. II, 531 (1959).
[12] P. S. Pinkney, *Ibid.* 116.
[13] H. Biersäugel, J. M. Akkermans, J. C. L. Armande and U. K. Pandit, *Recl. Trav. Chim. Pays-Bas* **95**, 266 (1976); A. G. Sanchez and J. Ballanato, *J. Chem. Soc.* Perkin II, 1561 (1975).
[14] F. W. Wehrli and T. Wirthlin, *Interpretation of Carbon-13 NMR Spectra*, p. 41. Heyden, London (1978).
[15] M. P. Strobel, L. Morin, D. Paquer and C. C. Pham, *Nouv. J. Chim.* **5**, 27 (1971).
[16] D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry*, p. 56. McGraw-Hill, London (1973).
[17] R. Jacquier and R. Zagdoun, *Bull. Soc. Chim. Fr.* **19**, 698 (1952).
[18] B. Lythgoe, S. Trippett and J. C. Watkins, *J. Chem. Soc.* 4060 (1956).
[19] A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.* **75**, 939 (1953).
[20] S. S. Pizey, *Synthetic Reagents*, Vol. I, pp. 176, 185. Ellis Horwood, Chichester (1974).
[21] R. E. Klinck and J. B. Stothers, *Can. J. Chem.* **44**, 45 (1966).
[22] *Fed. Regist.* **33**, 10569 (1968); *Chem. Abstr.* **69**, 58428m (1968).
[23] H. Rutzen and A. Loewenstein, *Ger.* 1,173,614; *Chem. Abstr.* **65**, PC 2062g (1966).
[24] M. Gocmen, G. Soussan and P. Fréon, *Bull. Soc. Chim. Fr.* 1310 (1973).
[25] J. P. Marino and D. M. Floyd, *Tetrahedron Letters* 3897 (1975).
[26] Ref. 10, p. 93.
[27] B. Castro and C. Selve, *Bull. Soc. Chim. Fr.* 4368 (1971).