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# Enamine Chemistry. XXVII.* Reduction of Enaminones, Enaminothiones and Thioamides by $LiAlH_4$ and $NaBH_4$

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Enamines, *1*, prepared from cycloalkanones, (cyclopentanone and cyclohexanone), and secondary amines (pyrrolidine, piperidine and morpholine), are reacted with phenylisocyanate and phenylisothiocyanate to give inseparable mixtures of enaminones (enaminothiones) *2* and enamino carboxanilides (thiocarboxanilides), *2'*. Reduction of compounds *2a* and *b* with LAH affords 1-(*N*-phenyl)-aminomethylcyclopentene, *4*, whereas reduction of compound *2c* yields three compounds, *4*–*6*. Reaction of compounds *2a*–*d* with $NaBH_4$ in refluxing acetonitrile affords compounds *7a*–*d* and further reduction of compound *7b* with $NaBH_4$ gives 1-(*N*-phenyl)aminomethyl-2-(1-piperidino)cyclopentane, *8b*. The thiocompound *2e* is reduced by LAH, to give compound *4*, whereas $NaBH_4$ produces a mixture of *N*-phenylcyclopentanethiocarboxamide, *9*, and (*N*-phenyl)aminomethylcyclopentane, *10*. Reduction of *N,N*-disubstituted thioamides, *11* with $NaBH_4$ produces disulfides, mercaptans and amines. Mechanistic considerations are presented.

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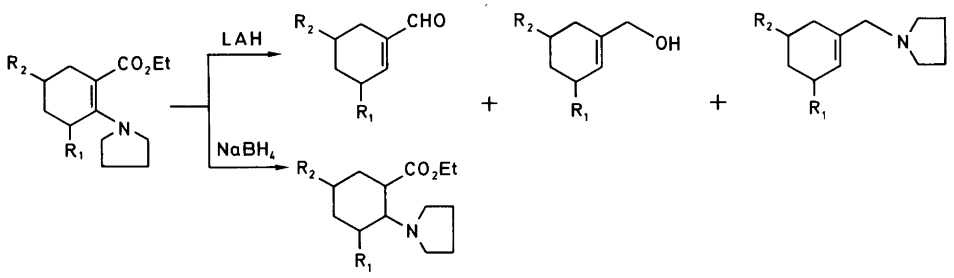
Recently,[1] the reduction of some enaminones[2] by lithium aluminium hydride (LAH) and sodium borohydride has given some unexpected results (Scheme 1) and especially the formation of unsaturated aldehydes is noteworthy. In continuation of our earlier work, this paper will report the reduction of another type of enaminones (vinylogous ureas and thioureas) and also $NaBH_4$-reduction of thioamides.

## RESULTS AND DISCUSSIONS

The starting enamines, *1*, are prepared according to the literature.[3–5] By reacting *1* with phenylisocyanate and phenylisothiocyanate in acetone or benzene at room temperature,[6,7] the products, *2,2'*, are smoothly isolated in good yields. Pyrrolidinocyclopentene, *1a*, and piperidinocyclopentene, *1b*, produce only the enaminones *2a* and *2b*, respectively, (no vinylic proton observed, *cf.* Table 1). However, the morpholino derivatives, *1c–d*, give a mixture of two isomers, *2c–d* and *2'c–d* and from their $^1H$ NMR spectra (Table 1 and Scheme 2)




*Scheme 1.*

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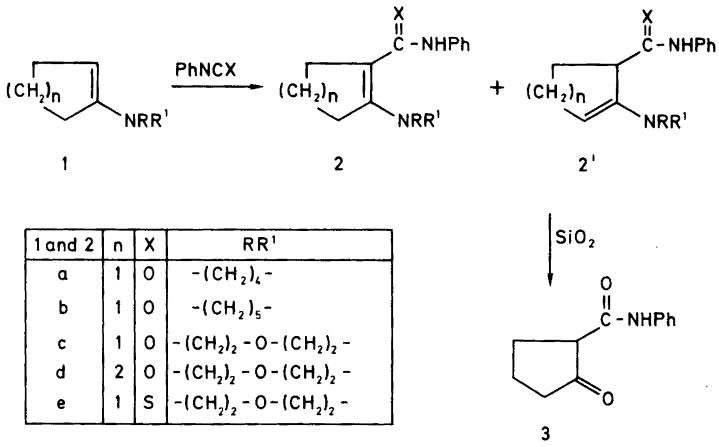



| 1 and 2 | n | X | RR' |
|---|---|---|---|
| a | 1 | O | $-(CH_2)_4-$ |
| b | 1 | O | $-(CH_2)_5-$ |
| c | 1 | O | $-(CH_2)_2-O-(CH_2)_2-$ |
| d | 2 | O | $-(CH_2)_2-O-(CH_2)_2-$ |
| e | 1 | S | $-(CH_2)_2-O-(CH_2)_2-$ |

*Scheme 2.*

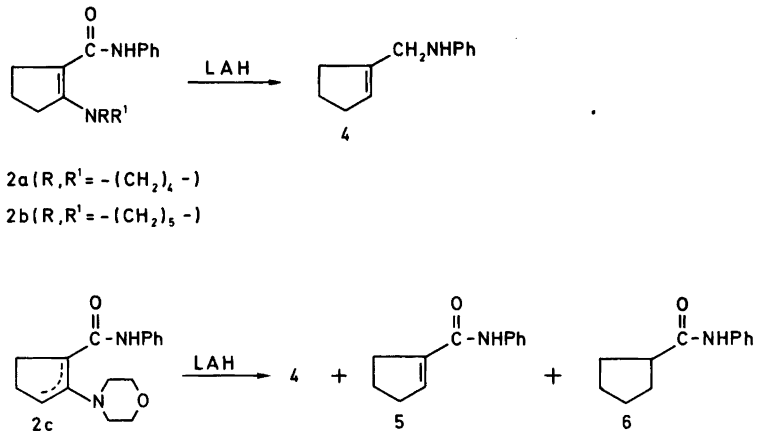
the ratios *2c/2'c*, *2d/2'd* and *2e/2'e* are found to be 38/62, 47/53 and 1/1, respectively.

Attempts to separate the two isomers *2c* and *2'c* (Scheme 2) using silica gel-column chromatography give only the hydrolysis product, *N*-phenyl-2-oxo-cyclopentanecarboxamide,[8] *3*.

Reduction of 2-(1-pyrrolidino)cyclopentene-1-(*N*-phenyl)carboxamide, *2a*, and 2-(1-piperidino)cyclopentene-1-(*N*-phenyl)carboxamide, *2b*, with LAH in refluxing tetrahydrofuran affords 1-(*N*-phenyl)aminomethylcyclopentene, *4*, in 16 and 24 % yields, respectively, whose spectroscopical and analytical data (see Experimental) are clearly consistent with the assigned structure. Thus, in IR absorption at 3550 $cm^{-1}$ (NH) is observed, in $^1H$ NMR there is one vinylic hydrogen ($\delta$ 5.52) and in the $^{13}C$ NMR spectra the vinylic carbons are observed at $\delta$ 125.61 and 142.18. Besides precise measurements MS also shows the expected fragmentation pattern, *e.g.* an allylic scission to give *m/e* 81 ($M^+ - 92$). Reduction of 2-(1-morpholino)cyclopentene-1-(*N*-phenyl) carboxamide, *2c*, with LAH in refluxing tetrahydrofuran affords compound *4* as main product (33 %; Scheme 3). Thus, a number of by-products are

*Table 1.* $^1H$ NMR spectra of the compounds *2a–e* and *2'a–e*.

| *2* and *2'* | $\delta$ ($CDCl_3$) |
|---|---|
| *a* | 8.71 (s, 1H) NH, 7.70–7.00 (m, 5H) Ph, 3.48 (t, *J* 6.5 Hz, 4H) $CH_2$-N-$CH_2$, 2.95–2.63 (m, 2H), 2.60–2.30 (m, 2H), 2.08–1.68 (m, 6H) |
| *b* | 9.63 (s, 1H) NH, 7.68–6.75 (m, 5H) Ph, 2.95–2.50 (m, 4H), 2.50–2.05 (m, 4H), 1.92–1.28 (m, 8H) |
| *c* | 9.90 (s, 0.62 H) NH, 9.00 (s, 0.38H) NH, 7.68–6.90 (m, 5H) Ph, 4.79 (t, *J* 1 Hz, 0.38H)C=CH, 3.90–3.30 (m, 4H) $CH_2OCH_2$, 3.11–1.52 (m, 10H) |
| *d* | 12.22, 9.80 (s, 1H) NH, 7.78–6.98 (m, 5H) Ph, 5.10 (t, *J* 4 Hz, 0.47H)C=CH, 3.93–3.53 (m, 4H) $CH_2OCH_2$, 3.30–1.32 (m, 12H) |
| *e* | 11.58 (s, 1H) NH, 7.85–7.00 (m, 5H) Ph, 3.80–3.42 (t, *J* 4 Hz, 4H), 4.80 (t, *J* 2 Hz, 0.5H), 3.00–2.20 (m, 8H), 2.00–1.50 (m, 2H) |

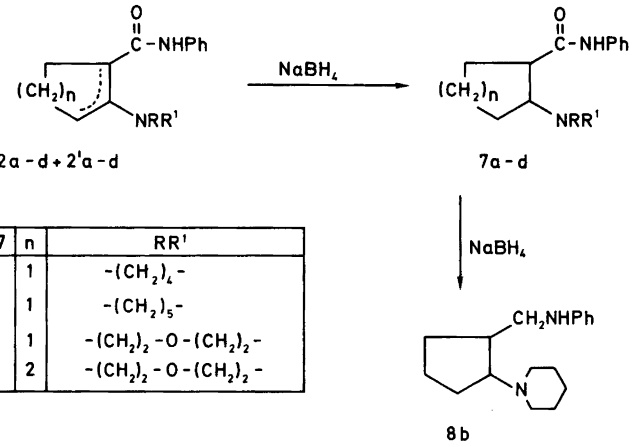



*Scheme 3.*

observed, two of them are isolated which are *N*-phenylcyclopentene-1-carboxamide,[9] *5*, (6%) and *N*-phenylcyclopentanecarboxamide,[10] *6*, (1%). The structures of the known compounds *5*[9] and *6*[10] are also proved by spectroscopy and precise mass measurements (*cf.* Experimental). As to the mechanism for the formation of *4*–*6* it is suggested that compound *5* is formed from *2c* by 1,4–$H^-$ addition followed by elimination of the amine. Compound *5* by another $H^-$ 1,2-addition. Similarly, *5* gives *6*.

The compounds *2a–d* are also reduced by $NaBH_4$ in refluxing acetonitrile to give cyclopentane and cyclohexane carboxanilides, *7a–d*, respectively, in good yields. These results are in accordance with a similar and exclusive 1,4-reduction of enaminones.[1] Further reduction of 2-(1-piperidino)cyclopentane-1-(*N*-phenyl)carboxamide, *2d*, with $NaBH_4$, *7b*, produces 1-(*N*-phenyl)aminoethyl-2-(1-piperidino)cyclopentane, *8b*, in 72 % yield. The structures of the reduced products are confirmed by precise mass measurements, $^1H$ NMR and IR spectra (Scheme 4, Table 2). The *7b*→*8b* reduction is unexpected since amides to our knowledge are not reduced by $NaBH_4$ alone (for other methods of amide reductions: $NaBH_4 + CH_3SO_3H$,[11] or $NaBH_4$ + transition metal salts[12]).

Also *2e*+*2'e* (Scheme 4) are reduced by LAH in refluxing THF to give a mixture of products, of which only compound *4* is isolated in 25 % yield. Reduction of *2e*+*2'e* by $NaBH_4$ in refluxing acetonitrile produces *N*-phenylcyclopentanethio-




| 2 and 7 | n | RR¹ |
|---|---|---|
| a | 1 | -(CH₂)₄- |
| b | 1 | -(CH₂)₅- |
| c | 1 | -(CH₂)₂-O-(CH₂)₂- |
| d | 2 | -(CH₂)₂-O-(CH₂)₂- |

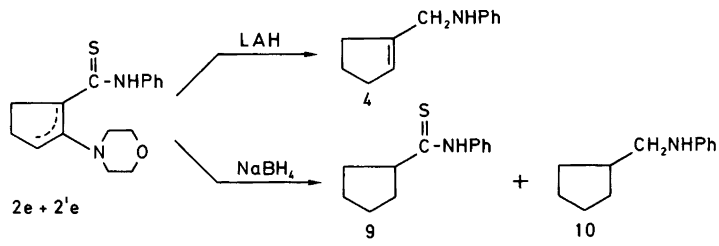
*Scheme 4.*

*Table 2.* Experimental data for compounds *7a–d* and *8*.

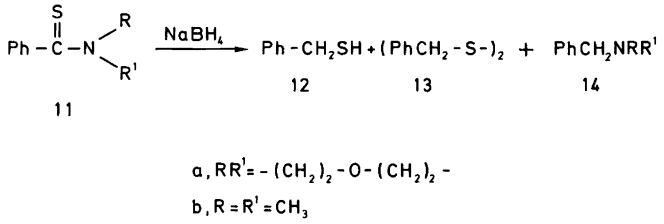
| Compound | Yield (%) | M.p. (°C) | MS: *m/e* (rel.int. %) | $^1$H NMR ($CDCl_3$) $\delta$ | IR ($cm^{-1}$) |
|---|---|---|---|---|---|
| *7a* | 84 | 80 | 258 ($M^+$, 100), 201(36), 187(16), 156(38), 138 (45). Precise measurement on *m/e* 258 (calc. for $C_{16}H_{22}N_2O$: 258.1733, found: 258.1733) | 12.30 (s, 1H) NH, 7.70–6.93 (m, 5H) Ph, 3.00–2.33 (m, 6H), 2.12–1.68 (m, 10H) | NH, 3400 CO, 1680 |
| *7b* | 100 | 162 | 272 ($M^+$, 52), 180(10), 152(86), 125(100). Precise measurement on *m/e* 272 (calc. for $C_{17}H_{24}N_2O$: 272.18889, found: 272.1888) | 12.40 (s, 1H) NH, 7.70–6.80 (m, 5H) Ph, 3.00–2.35 (m, 6H), 2.19–1.00 (m, 12H) | NH, 3250 CO, 1700 |
| *7c* | 70 | 100 | 274 ($M^+$, 100), 257(12), 232(17), 182(19), 126 (60). Precise measurement on *m/e* 274 (calc. for $C_{16}H_{22}N_2O_2$: 274.1682. found: 274.1680) | 11.82 (s, 1H) NH, 6.80–7.68 (m, 5H) Ph, 4.05–3.38 (t, *J* 15 Hz, 4H) 3.09–2.20 (m, 6H), 1.32–1.82 (m, 6H) | NH, 3300 CO, 1700 |
| *7d* | 70 | 145 | 288 ($M^+$, 65), 245(29), 194(27), 166(32), 126 (100). Precise measurement on *m/e* 288 (calc. for $C_{17}H_{24}N_2O_2$: 288.1838, found: 288.1837) | 11.80 (s, 1H) NH, 7.70–6.81 (m, 5H) Ph, 3.92–3.52 (t, *J* 4 Hz, 4H) $CH_2OCH_2$, 3.03–2.13 (m, 6H), 2.13–0.90 (m, 8H) | NH, 3480 CO, 1705 |
| *8b* | 72 | | 258 ($M^+$, 100), 173(49), 166(98), 124(98). Precise measurement on *m/e* 258 (calc. for $C_{17}H_{26}N_2O$: 258.2091, found: 258.2096) | 7.20–6.30 (m, 5H) Ph 3.20–2.78 (m, 2H), 2.68–2.10 (m, 4H), 1.92–0.70 (m, 14H) | NH, 3250 |

carboxamide,[13] *9*, and (*N*-phenyl)aminomethylcyclopentane,[14] *10*, in 33% and 2% yields, respectively, (Scheme 5), the structures of which are confirmed by spectral and analytical data. Compound *9* is suggested to be formed from *2e* by 1,4-hydride addition, elimination of morpholine and subsequently another 1,4-reduction. Compound *10* is produced from *9* by a simple reduction (C=S→ >$CH_2$).

As to the reduction of *2e*+*2'e* with $NaBH_4$ no disulfides or mercaptans are isolated, which is contrary to a recent note[15] on $NaBH_4$-reduction of




*Scheme 5.*




*Scheme 6.*

certain simple thioamides (Scheme 5). Only the solid products have been isolated, according to the above cited note, without mentioning the reaction time and temperature. So we are strongly prompted to investigate the same reaction on a few simple thioamides which are of special interest.

It has now been found that the reduction of thioamides (*11*, $RR' = -(CH_2)_2-O-(CH_2)_2-$ or $-(CH_3)_2$) with $NaBH_4$ in refluxing isopropanol gives a mixture of three compounds: The corresponding mercaptans, *12*, disulfides, *13* and amines, *14*, in reasonable yields. Higher yields of all products are found with acetonitrile as solvent. Running the experiments in an inert atmosphere ($N_2$) does not give any change of product composition. (*cf.* Experimental, Scheme 6).

To our knowledge *N,N*-disubstituted thioamides have not been reduced by $NaBH_4$ to amines or to mercaptans. It is also observed (Experimental) that the yield of mercaptan is increased and that of disulfide is decreased at longer reaction time due to the known $NaBH_4$ reduction of disulphides.[16-19] As to the mechanism it is suggested that the first step is a 1,2-hydride addition to the thiocarbonyl group to give a salt of a semithioaminal, which subsequently produces the amine and mercaptan. *N*-Monosubstituted thioamides (*e.g.* thiobenzanilide[20]) give a complex product composition when reacted with $NaBH_4$ (for reduction of such thio-amides as *S*-salts, see Refs. 21 and 22).

## EXPERIMENTAL

$^1H$ 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 $\delta$-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. M.p.s are uncorrected.

*Starting materials.* The enamines *1* are prepared by known methods.[3-5] Enamine carboxamides, enaminone carboxamides and thioanalogues, *2*, are obtained by the reaction of enamines *1* with phenylisocyanate and phenylisothiocyanate (0.01 mol: 0.01 mol) in an anhydrous solvent. Compounds *2c–d* are known.[6,7]

*Compound* 2a. 2-(1-Pyrrolidino)cyclopentene-1-(*N*-phenyl)-carboxamide. Benzene (30 ml), 20 min. Yield: 82 %. M.p. 138 °C ($C_6H_6$). Precise measurement of $M^+$ (calc. for $C_{16}H_{20}N_2O$, 256.1576, found: 256.1576). MS: *m/e* (rel.int. %): 2.56 ($M^+$, 100), 164 (49), 136 (29), 93 (71). $^1H$ NMR ($CDCl_3$): $\delta$ 8.71 (s, 1H) NH, 7.70–7.00 (m, 5H) Ph, 3.48 (t, *J* 6.5 Hz, 4H), $CH_2NCH_2$, 2.95–2.63 (m, 2H), 2.60–2.30 (m, 2H), 2.08–1.68 (m, 6H). IR ($cm^{-1}$) KBr: 1700 (C=O), 3300 (NH).

*Compound* 2b. 2-(1-Piperidino)cyclopentene-1-(*N*-phenyl)-carboxamide. Acetone (3 ml), 30 min. Yield: 98 %. M.p. 102 °C (ether). Precise measurements of $M^+$ (calc. for $C_{17}H_{22}N_2O$, 270.1733, found: 270.1731. MS: *m/e* (rel.int. %): 270 ($M^+$, 73), 203 (41), 178 (100), 150 (47), 93 (69), 74 (62). $^1H$ NMR ($CDCl_3$): $\delta$ 9.63 (s, 1H) NH, 7.68–6.75 (m, 5H) Ph, 2.95–2.50 (m, 4H), 2.50–2.05 (m, 4H), 1.92–1.28 (m, 7H). IR ($cm^{-1}$) KBr: 1670 (C=O), 3500 (NH).

*General procedure of reduction with LAH.* Enamine-derivatives (2+2'; 0.01 mol) are added dropwise on stirring to the ice-cooled mixture of LAH (0.03 mol) in anhydrous THF (100 ml) under $N_2$ atmosphere. The reaction mixture is refluxed for 1 h after the addition.

*Work-up procedure.* At 0 °C 1.14 g $H_2O$ is added dropwise followed by 0.85 g of 30 % NaOH + 8.5 g $H_2O$. The ice-bath is removed and stirring is continued for 20 min. The mixture is then filtered, extracted with ether and dried ($MgSO_4$), the solvent is evaporated under reduced pressure and the product is purified on silica gel plates using 50 % ether–light petroleum as eluent.

*Compound* 4. 1-(*N*-Phenyl)aminomethylcyclopentene. Precise measurement of $M^+/e$: 173 (calc. for $C_{12}H_{15}N$, 173.1204, found: 173.1205). MS: *m/e*

(rel.int. %): 173 ($M^+$, 100), 107 (41), 93 (59), 81 (29), 77 (29). $^1H$ NMR ($CDCl_3$): $\delta$ 7.30–6.39 (m, 5H) Ph, 5.52 (t, $J$ 3 Hz, 1H) C=CH, 3.68 (s, 2H), 2.50–1.42 (m, 6H). IR($cm^{-1}$): 3550 (NH).

*Compound* 5. Cyclopentene-1-(*N*-phenyl)carboxamide,[9] m.p. 125 °C (lit.[9] 126 °C), yield: 6 %, precise measurement of $M^+$ (calc. for $C_{12}H_{13}NO$, 187.0997, found: 187.0997). IR ($cm^{-1}$) KBr: 1725 (C=O), 3400 (NH).

*Compound* 6. *N*-Phenylcyclopentanecarboxamide,[10] m.p. 160 °C (lit.[10] 160.1–161.2 °C), yield: 1%, precise measurement of $M^+$ (calc. for $C_{12}H_{15}NO$, 189.1153, found: 189.1155). IR ($cm^{-1}$) KBr: 1725 (C=O), 3300 (NH).

*General procedure for reduction with $NaBH_4$.* Sodium borohydride (0.03 mol) and enamine-derivatives (2+2′; 0.01 mol in acetonitrile (30 ml) are refluxed for 1 h.

*Work-up procedure.* To the ice-cooled reaction mixture, 1.14 g $H_2O$ is added dropwise followed by 0.85 g of 30 % NaOH + 8.5 g $H_2O$. The ice-bath is removed and the mixture dried ($MgSO_4$); then the solvent is evaporated under reduced pressure and the product purified by crystallization from ether–light petroleum.

*Compounds* 7a–d *and* 8: (*cf.* Table 2).

*Compound* 9. *N*-Phenylcyclopentanethiocarboxamide,[11] m.p. 75 °C (lit.[11] 80 °C). Precise measurement of $M^+$ (calc. for $C_{12}H_{15}NS$, 205.0925, found: 205.0925). MS: *m/e* (rel. int. %): 205 ($M^+$, 92), 172(100), 164(87), 130(27). $^1H$ NMR ($CDCl_3$): $\delta$ 9.01 (s, 1H) NH, 7.70–6.90 (m, 5H) Ph, 3.28–2.63 (m, 1H), 2.20–1.18 (m, 8H). IR ($cm^{-1}$) KBr: 3400 (NH).

*Compound* 10. (*N*-Phenyl)aminomethylcyclopentane,[12] yield: 2 %. Precise measurements on $M^+$ (calc. for $C_{12}H_{17}N$, 175.1361, found: 175.1361). MS: *m/e* (rel.int. %): 175 ($M^+$, 20), 106 (100). IR ($cm^{-1}$): 3400 (NH).

*Reduction of thioamide* 11a *with $NaBH_4$.* Sodium borohydride (1.14 g, 0.03 mol) is added to a solution of thioamide, *11a*, (2.07 g, 0.01 mol) in isopropanol (20 ml) and the mixture is refluxed for 3 h. The solvent is evaporated under reduced pressure and water (25 ml) is added to the reaction mixture. The products are extracted several times with $CH_2Cl_2$, the organic layer is extracted with dil. NaOH to separate benzyl mercaptane,[23] *12a*, as sodium salt (water phase) and on acidification, it is isolated in 31 % yield. The $CH_2Cl_2$ layer is then extracted again with dil. $H_2SO_4$ to separate benzyl morpholine,[24] *14a*, as sulfate (27 %). The $CH_2Cl_2$ layer is finally washed with water and dried ($MgSO_4$), the solvent is evaporated to yield dibenzyl disulfide,[15–19] *13a*, in 28 % yield.

The products are in all respects identical with authentic samples.

Reduction of the same thioamide, *11a*, in refluxing acetonitrile (2 h) (TLC) as described above produces benzyl mercaptan, benzyl morpholine and dibenzyl disulfide in 55, 22 and 14 % yields, respectively.

*Reduction of the thioamide* 11b *with $NaBH_4$ in acetonitrile. 11b* is reduced as above for 26 h under reflux (TLC) to yield benzyl mercaptan, *12a*, (68 %). *N,N*-Dimethylbenzylamine,[25] (23 %) *14b* and dibenzyl disulfide, *13a*, (6 %). The three products are identical in all respects with authentic samples.

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