Alkynylation of Thiolactams. New Synthesis of α-Substituted Pyrrolidine and Piperidine Alkaloids

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Alkynylation of *S*-alkylthioamidium salts of thiolactams with lithium acetylides followed by reduction with $LiAlH_4$ provided α-alkynylazacycloalkanes, which on reduction, or hydroboration followed by oxidation, gave α-substituted pyrrolidine and piperidine alkaloids.

The development of functionalization methods for azacycloalkanes such as pyrrolidines, piperidines, and perhydroazepines is of great importance in the synthesis of naturally occurring alkaloids.[1] In connection with our studies on the utilization of the thioamide group in organic synthesis,[2] we describe the alkynylation of thiolactams, and subsequent manipulation leading to α-substituted pyrrolidine and piperidine alkaloids.

The thioamide group has increasingly been recognized as a useful synthon in organic synthesis. Recently, the attack of organolithium reagents upon the carbon-sulphur double bond of thioamides has been explored.[3] Unfortunately, initial attempts at alkynylation of pyrrolidine-2-thione by treatment with lithium acetylides were unsuccessful. Previously, we described the carbon-carbon bond forming reaction of *S*-alkylthioamidium salts with malononitrile.[4] Here we describe the reaction[5] of *S*-alkylthioamidium salts, prepared from thiolactams by treatment with methyl iodide, with lithium acetylide, followed by reduction with lithium aluminium hydride ($LiAlH_4$) to give α-alkynylazacycloalkanes.

Thus, *S*-methylthioamidium salts (**I**), generated *in situ* from thiolactams (**1**)—(**3**) and methyl iodide in tetrahydrofuran (THF) at room temperature for 8 h, were treated with a lithium acetylide (**6**)—(**8**) at −78 °C. The resulting adducts (**II**) were then treated with $LiAlH_4$ at −78 °C followed by warming to −20 °C to give the α-alkynylazacycloalkanes (**10**)—(**17**) in moderate yields (Table, entries 1—8). Similarly, the α-alkynylazacycloalkanes (**18**)—(**22**) were obtained from *N*-benzylthiolactams (**4**) and (**5**) (Table, entries 9—13).

Our attention was focussed on the synthesis of pyrrolidine and piperidine alkaloids by the elaboration (reduction or hydroboration) of the acetylene function. Hydrogenation of piperidinylacetylene (**17**) in the presence of palladium hydroxide [$Pd(OH)_2$] in methanol afforded (±)-*N*-methylconiine‡ (**23**) quantitatively. Under the same conditions the *N*-benzyl derivative (**21**) underwent both reduction and hydrogenolysis[6] to provide (±)-coniine (**24**)‡ quantitatively.

Hydroboration-oxidation of acetylenes is an effective procedure for regioselective ketone synthesis. However, to our knowledge, the hydroboration of acetylenic amines has scarcely been studied.[7] Monohydroboration of piperidinylacetylene (**17**) with bis(1,2-dimethylpropyl)borane§ in THF at 0 °C followed by oxidative work-up proceeded in a regioselective manner,

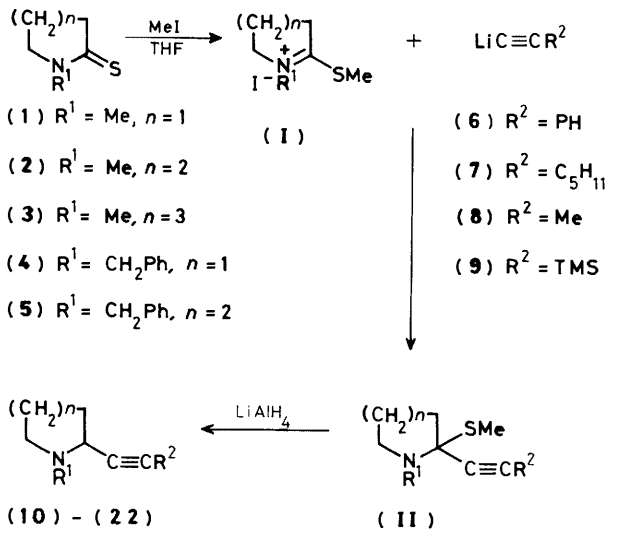

Table. Isolated yields of α-alkynylazacycloalkanes from thiolactams (three-steps sequence)

Entry	Product	R^1	R^2	*n*	Yield (%)
1	(**10**)	Me	Ph	1	70
2	(**11**)	Me	Ph	2	67
3	(**12**)	Me	Ph	3	80
4	(**13**)	Me	n-C_5H_{11}	1	71
5	(**14**)	Me	n-C_5H_{11}	2	74
6	(**15**)	Me	n-C_5H_{11}	3	55
7	(**16**)	Me	Me	1	61
8	(**17**)	Me	Me	2	85
9	(**18**)	CH_2Ph	Ph	1	78
10	(**19**)	CH_2Ph	n-C_5H_{11}	1	67
11	(**20**)	CH_2Ph	Me	1	66
12	(**21**)	CH_2Ph	Me	2	65
13	(**22**)	CH_2Ph	TMS	1	80

with ketone formation at the less hindered carbon atom of the triple bond to give (±)-*N*-methylpelletierine (**25**) as a major product (50% yield), and its regioisomer (**26**) (14%). However, the regioselectivity (3.5:1) is not high compared with that (91:9) for the hydroboration of cyclohexylethyne.[8] This somewhat low regioselectivity may be due to co-ordination of the boron of the bis(1,2-dimethylpropyl)borane with the amine of the piperidine

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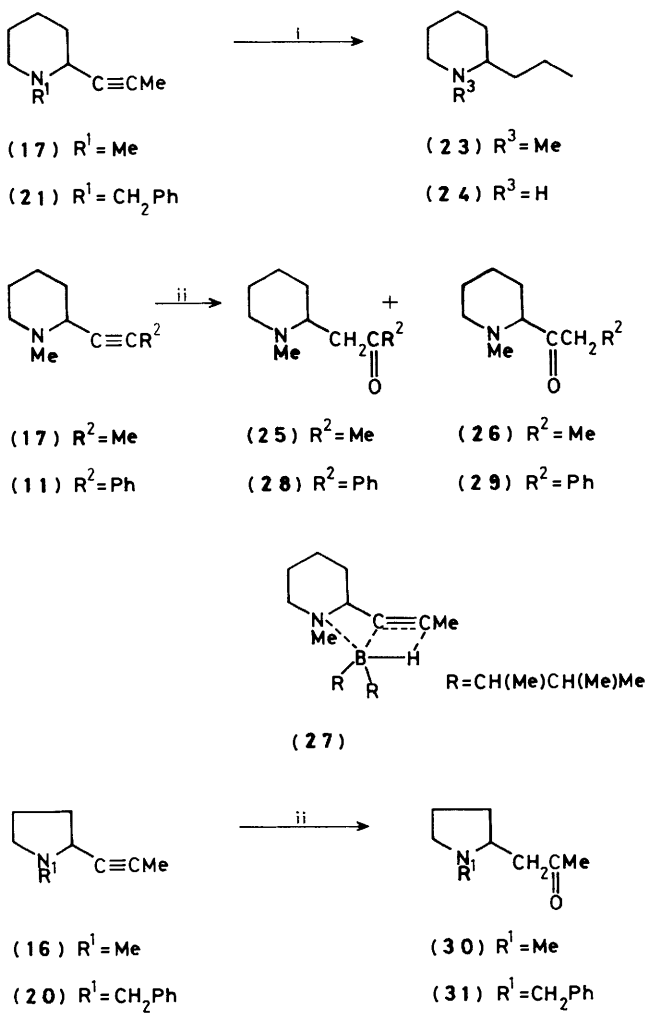
‡ Melting points of derivatives of these compounds were consistent with those described in the literature; see Experimental section.

§ Although treatment of (**17**) with 9-borabicyclo[3.3.1]nonane caused no reaction at room temperature, refluxing in THF provided (**25**) (34%) and (**26**) (33%) with no regioselectivity.



Scheme. (i) $Pd(OH)_2, H_2$; (ii) 1. bis(1,2-dimethylpropyl)borane, 2. H_2O_2/-NaOH

as in (**27**). Similarly, (±)-sedaminone (**28**)* was obtained from (**11**) (50% yield), together with its regioisomer (**29**) (18%). On the other hand, hydroboration of the pyrrolidinylacetylene (**16**) showed higher regioselectivity than the piperidinyl analogue (**17**), providing (±)-hygrine (**30**) (54%) on oxidation. Similarly, the reaction of (**20**) proceeded regiospecifically to afford only (**31**), in 52% yield. This suggested that co-ordination of the boron of bis(1,2-dimethylpropyl)borane with the pyrrolidine nitrogen was difficult, presumably due to steric hindrance between the nitrogen substituent and the dialkyl group of the diborane.

In summary, the present study provides a convenient and simple procedure for the synthesis of α-alkynylazacycloalkanes, which are transformed into α-substituted pyrrolidine and piperidine alkaloids. This method should be applicable to the synthesis of many kinds of α,α′-disubstituted pyrrolidine and piperidine alkaloids[10] such as ant venom, and its application is now in progress.

Experimental

M.p.s and b.p.s are uncorrected. M.p.s were measured with a Yanaco micro melting point apparatus and b.p.s were measured with a Buchi Kugelrohr apparatus. I.r. spectra were determined with a JASCO A-102 spectrophotometer. ^{1}H N.m.r. spectra were run on a JEOL PMX-60 (60 MHz) or JX-270 (270 MHz) spectrometer using $CDCl_3$ as a solvent. Mass spectra were measured with a JEOL JMS-D200 spectrometer.

General Procedure for Preparation of α-Alkynylazacycloalkanes (**10**—**22**).—A mixture of thiolactam (**1**)—(**5**) (5 mmol) and iodomethane (8 mmol) in THF (10 ml) was stirred at room temperature for 6 h under argon. The reaction mixture was cooled −78 °C, and to it was added a solution of lithium acetylide (**6**)—(**9**), prepared by the dropwise addition of butyllithium (1.6M in hexane, 3.75 ml, 6 mmol) to acetylene (6 mmol) in THF (5 ml) at −78 °C. The mixture was then allowed to warm to −20 °C over 2 h when $LiAlH_4$ (500 mg, 13 mmol) at the same temperature was added. The mixture was stirred for a further hour at −10 °C when 10% aqueous sodium hydroxide (10 ml) was added to it; the mixture was then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. Bulb-to-bulb distillation of the crude product using Kugelrhor apparatus yielded the α-azacycloalkanes (**10**)—(**22**) (see Table).

1-(1-*Methylpyrrolidin-2-yl*)-2-*phenylacetylene* (**10**). B.p. 72—79 °C at 0.5 mmHg (Found: C, 82.3; H, 8.1; N, 7.5. $C_{13}H_{15}N$ requires C, 82.5; H, 8.2; N, 7.6%); $\nu_{max.}$(neat) 2 200 and 1 595 cm^{-1}; δ_H($CDCl_3$) 1.47—3.14 (m, 6 H), 2.50 (s, 3 H, NMe), 3.14—3.47 (m, 1 H, NCH), and 7.00—7.57 (m, 5 H, Ph).

1-(1-*Methylpiperidin-2-yl*)-2-*phenylacetylene* (**11**). B.p. 82—87 °C at 0.5 mmHg (Found: C, 84.2; H, 8.6; N, 6.8. $C_{14}H_{17}N$ requires C, 84.4; H, 8.6; N, 7.0%); $\nu_{max.}$(neat) 2 200 and 1 595 cm^{-1}; δ_H($CDCl_3$) 1.13—2.10 (m, 6 H), 2.10—2.90 (m, 2 H), 2.24 (s, 3 H, NMe), 3.54 (t, *J* 4 Hz, 1 H, NCH), and 7.10—7.60 (m, 5 H, Ph).

1-(1-*Methylperhydroazepin-2-yl*)-2-*phenylacetylene* (**12**). B.p. 90—95 °C at 0.5 mmHg (Found: C, 84.8; H, 8.7; N, 6.3. $C_{15}H_{19}N$ requires C, 84.45; H, 9.0; N, 6.6%); $\nu_{max.}$(neat) 2 200 and 1 595 cm^{-1}; δ_H($CDCl_3$) 1.50—2.27 (m, 8 H), 2.27—3.00 (m, 2 H, NCH_2), 2.50 (s, 3 H, NMe), 3.67—3.97 (m, 1 H, NCH), and 7.13—7.63 (m, 5 H, Ph).

1-(1-*Methylpyrrolidin-2-yl*)*hept*-1-*yne* (**13**). B.p. 54—58 °C at 0.6 mmHg (Found: C, 80.0; H, 11.8; N, 7.5. $C_{12}H_{21}N$ requires C, 80.4; H, 11.8; N, 7.8%); $\nu_{max.}$(neat) 2 220 cm^{-1}; δ_H($CDCl_3$) 0.60 (m, 3 H, Me), 1.03—2.50 (m, 14 H), 2.37 (s, 3 H, NMe), and 2.50—3.57 (m, 1 H, NCH).

1-(1-*Methylpiperidin-2-yl*)*hept*-1-*yne* (**14**). B.p. 59—62 °C at 0.5 mmHg (Found: C, 80.5; H, 12.1; N, 7.0. $C_{13}H_{23}N$ requires C, 80.8; H, 12.0; N, 7.25%); $\nu_{max.}$(neat) 2 225 cm^{-1}; δ_H($CDCl_3$) 0.67—1.04 (m, 3 H, Me), 1.04—2.63 (m, 16 H), 2.37 (s, 3 H, NMe), and 3.00—3.38 (m, 1 H, NCH).

1-(1-*Methylperhydroazepin-2-yl*)*hept*-1-*yne* (**15**). B.p. 68—70 °C at 0.5 mmHg (Found: C, 79.6; H, 12.15; N, 6.3. $C_{14}H_{25}N$ requires C, 81.1; H, 12.15; N, 6.8%); $\nu_{max.}$(neat) 2 200 cm^{-1}; δ_H($CDCl_3$) 0.60—1.04 (m, 3 H, Me), 1.04—2.80 (m, 18 H), 2.40 (s, 3 H, Me), and 3.33—3.77 (m, 1 H, NCH).

1-(1-*Methylpyrrolydin-2-yl*)*prop*-1-*yne* (**16**). B.p. 68—71 °C at 17 mmHg (Found: M^+, 123.1049. $C_8H_{13}N$ requires *M*, 123.1047); $\nu_{max.}$(neat) 2 230 cm^{-1}; δ_H($CDCl_3$) 1.60—2.70 (m, 5 H), 1.85 (d, *J* 2 Hz, 3 H, Me), 2.41 (s, 3 H, NMe), and 2.70—3.30 (m, 1 H, NCH).

1-(1-*Methylpiperidin-2-yl*)*prop*-1-*yne* (**17**). B.p. 64—67 °C at 15 mmHg (Found: M^+, 137.1202. $C_9H_{15}N$ requires *M*, 137.1203); $\nu_{max.}$(neat) 2 230 cm^{-1}; δ_H($CDCl_3$) 1.10—2.00 (m, 6 H), 1.85 (d, *J* 2 Hz, 3 H, CH_2), 2.00—3.00 (m, 2 H, NCH_2), 2.83 (s, 3 H, NMe), and 3.00—3.33 (m, 1 H, NCH).

1-(1-*Benzylpyrrolidin-2-yl*)-2-*phenylacetylene* (**18**). B.p. 122—128 °C at 0.4 mmHg (Found: C, 87.5; H, 7.3; N, 5.5. $C_{19}H_{19}N$ requires C, 87.3; H, 7.3; N, 5.4%); $\nu_{max.}$(neat) 2 200 and 1 595 cm^{-1}; δ_H($CDCl_3$) 1.57—3.00 (m, 6 H), 3.60 and 4.08 (ABq, *J* 13 Hz, 2 H, CH_2Ph), 3.62 (m, 1 H, NCH), and 7.16—7.63 (m, 10 H, 2Ph).

* (±)-Sedaminone has previously been reduced to (±)-sedamine.[9]

1-(1-*Benzylpyrrolidin*-2-*yl*)*hept*-1-*yne* (**19**). B.p. 94—98 °C at 0.5 mmHg (Found: C, 84.8; H, 9.9; N, 5.2. $C_{18}H_{25}N$ requires C, 84.65; H, 9.9; N, 5.5%); $\nu_{max.}$(neat) 2 210 and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 0.64—1.10 (m, 3 H, Me), 1.10—3.33 (m, 14 H), 3.33—3.50 (m, 1 H, NCH), 3.47, 4.01 (ABq, *J* 13 Hz, 2 H, CH_2Ph), and 7.30 (s, 5 H, Ph).

1-(1-*Benzylpyrrolidin*-2-*yl*)*prop*-1-*yne* (**20**). B.p. 73—76 °C at 0.15 mmHg (Found: C, 83.3; H, 8.3; N, 7.1. $C_{14}H_{17}N{\cdot}0.1H_2O$ requires C, 83.6; H, 8.6; N, 7.0%; Found: M^+, 199.1347. $C_{14}H_{17}N$ requires *M*, 199.1359); $\nu_{max.}$(neat) 2 225 and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 1.50—3.07 (m, 6 H), 1.87 (d, *J* 2 Hz, 3 H, Me), 3.07—3.50 (m, 1 H, NCH), 3.45, 4.05 (ABq, *J* 13 Hz, 2 H, CH_2Ph), and 7.32 (s, 5 H, Ph).

1-(1-*Benzylpiperidin*-2-*yl*)*prop*-1-*yne* (**21**). B.p. 88—89 °C at 0.3 mmHg (Found: C, 84.6; H, 8.9; N, 6.5. $C_{15}H_{19}N$ requires C, 84.45; H, 9.0; N, 6.6%); $\nu_{max.}$(neat) 2 225 and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 1.00—2.10 (m, 6 H), 1.92 (d, *J* 2 Hz, 3 H, Me), 2.10—3.20 (m, 2 H, NCH_2), 3.20—3.80 (m, 1 H, NCH), 3.51, 3.77 (ABq, *J* 13 Hz, 2 H, CH_2Ph), and 7.10—7.54 (m, 5 H, Ph).

1-(1-*Benzylpyrrolidin*-2-*yl*)-2-*trimethylsilylacetylene* (**22**). B.p. 86—91 °C at 0.4 mmHg (Found: C, 74.9; H, 9.1; N, 5.6. $C_{16}H_{23}NSi$ requires C, 74.6; H, 9.0; N, 5.4%); $\nu_{max.}$(neat) 2 150 and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 0.22 (s, 9 H, $SiMe_3$), 1.53—2.23 (m, 4 H), 2.23—2.87 (m, 2 H, NCH_2), 3.16—3.20 (m, 1 H, NCH), 3.54, 4.05 (ABq, *J* 13 Hz, 2 H, CH_2Ph), and 7.37 (s, 5 H, Ph).

(±)-N-*Methylconiine* (**23**).—A mixture of (**17**) (45 mg) and $Pd(OH)_2$ [12] (14 mg) in methanol (3 ml) was stirred under hydrogen (1 atm) for 2.5 h. Filtration followed by washing of the residue with methanol and evaporation of the solvent yielded (**23**) (58 mg, 100%) as an oil; $\delta_H(CDCl_3)$ 0.67—1.04 (m, 3 H, Me), 1.04—2.33 (m, 12 H), 2.27 (s, 3 H, NMe), and 2.60—3.10 (m, 1 H, NCH); hydrochloride salt, m.p. 169—170 °C (acetone) (lit.,[12] 168—168.5 °C) (Found: C, 59.9; H, 11.2; N, 7.8. Calc. for $C_9H_{20}ClN{\cdot}0.1H_2O$: C, 60.2; H, 11.25; N, 7.8%).

(±)-*Coniine* (**24**).—A mixture of (**21**) (108 mg) and $Pd(OH)_2$ (10 mg) in methanol (3 ml) was stirred under hyrogen (1 atm) for 7 h, then worked-up by the method described for (**23**) to give (**24**) (81 mg, 100%) as an oil; $\nu_{max.}$ 3 300 and 1 650 cm^{-1}; $\delta_H(CDCl_3)$ 0.85 (br t, *J* 6 Hz, 3 H), and 2.00—3.30 (m, 3 H); i.r. and ^1H n.m.r. spectra were identical with those described in the literature.[13] The hydrochloride salt was crystallised from acetone–methanol, m.p. 219—220 °C (lit.,[12] 216—217 °C) (Found: C, 58.6; H, 11.1; N, 8.6. Calc. for $C_8H_{18}ClN$: C, 58.7; H, 11.1; N, 8.55%).

General Procedure for Monohydroboration and Oxidation of α-*Alkynylazacycloalkanes*.—To a stirred solution of bis(1,2-dimethylpropyl)borane (0.5 mmol), prepared from borane–THF complex (1.0M, 1.5 ml) and 2-methylbut-2-ene (3 mmol, 0.32 ml) by the method of H. C. Brown,[14] was added a solution of α-alkynylazacycloalkane (0.5 mmol) in THF (2 ml) at 0 °C. The mixture was kept in a refrigerator (5 °C) overnight after which it was quenched with 6M aqueous NaOH (0.3 ml) and 30% aqueous H_2O_2 (0.6 ml) at 0 °C; it was then stirred for an additional hour at room temperature. The reaction mixture was cooled to 0 °C, 10% hydrochloric acid (2 ml) was added and it was then stirred for 30 min at room temperature and washed with diethyl ether. The aqueous layer was made alkaline with K_2CO_3 and extracted with diethyl ether. The extract was dried (K_2CO_3) and concentrated, and the residue separated by alumina column chromatography (hexane–ethyl acetate, 30:1) to give the amino ketones.

(±)-N-*Methylpelletierine* (**25**) (50%). B.p. 67—69 °C at 15 mmHg (Found: M^+, 155.1288. $C_9H_{17}NO$ requires *M*, 155.1309); $\nu_{max.}$(neat) 1 710 cm^{-1}; $\delta_H(CDCl_3)$ 1.19—1.40 (m, 2 H), 1.47—1.68 (m, 4 H), 2.18 (s, 3 H, Me), 2.21 (s, 3 H, NMe), 2.11—2.45 (m, 2 H), 2.52—2.59 (m, 1 H), and 2.75—2.83 (m, 2 H). The hydrochloride salt was crystallised from ethyl acetate, m.p. 161.5—162.5 °C (lit.,[15] 158—159 °C) (Found: C, 56.4; H, 9.4; N, 7.3. Calc. for $C_9H_{18}ClNO$: C, 56.4; H, 9.5; N, 7.3%).

Ethyl 1-*methylpiperidin*-2-*yl ketone* (**26**) (14%). B.p. 65—67 °C at 15 mmHg (Found: M^+, 155.1303. $C_9H_{17}NO$ requires *M*, 155.1305); $\nu_{max.}$(neat) 1 710 cm^{-1}; $\delta_H(CDCl_3)$ 1.06 (t, *J* 7 Hz, 3 H, Me), 1.18—2.69 (m, 10 H), 2.13 (s, 3 H, NMe), and 2.90—2.95 (m, 1 H, NCH).

(±)-*Sedaminone* (**28**). 50%; b.p. 92—93 °C at 0.15 mmHg (lit.,[16] 135—136 °C at 1 mmHg) (Found: M^+, 217.1437. Calc. for $C_{14}H_{19}NO$: *M*, 217.1465); $\nu_{max.}$(neat) 1 680 and 1 595 cm^{-1}; $\delta_H(CDCl_3)$ 1.00—2.53 (m, 7 H), 2.32 (s, 3 H, NMe), 2.53—3.92 (m, 4 H), 7.30—8.20 (m, 5 H, Ph). Picrate, m.p. 159.5—161 °C (lit.,[16] 159—160 °C) (Found: C, 53.7; H, 5.0; N, 12.75. Calc. for $C_{20}H_{22}N_4O_8$: C, 53.8; H, 5.0; N, 12.55%).

Benzyl 1-*methylpiperidin*-2-*yl ketone* (**29**) (18%). B.p. 87—90 °C at 0.15 mmHg (Found: C, 77.0; H, 8.85; N, 6.6. $C_{14}H_{19}NO$ requires C, 77.4; H, 8.8; N, 6.45%); $\nu_{max.}$(neat) 1 715 and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 0.90—2.33 (m, 6 H), 2.13 (s, 3 H, NMe), 2.47—3.27 (m, 3 H, NCH and NCH_2), 3.83 (s, 2 H, CH_2Ph), and 7.34 (s, 5 H, Ph).

(±)-*Hygrine* (**30**) (54%). B.p. 71.5—75 °C at 15 mmHg; $\nu_{max.}$(neat) 1 710 cm^{-1}; $\delta_H(CDCl_3)$ 1.00—2.73 (m, 6 H), 2.13 (s, 3 H), 2.26 (s, 3 H), and 2.73—3.53 (m, 3 H). I.r. and ^1H n.m.r. spectra were identical with those described in the literature.[17] Picrate, m.p. 151—153 °C (ethanol) (lit.,[18] 153.5—155 °C) (Found: C, 45.4; H, 4.9; N, 15.4. Calc. for $C_{14}H_{18}N_4O_8$: C, 45.4; H, 4.9; N, 15.1%).

(±)-N-*Benzylhygrine* (**31**) (52%). B.p. 87.5—91.5 °C at 0.15 mmHg (Found: C, 77.6; H, 8.7; N, 6.2. $C_{14}H_{19}NO$ requires C, 77.4; H, 8.8; N, 6.45%); $\nu_{max.}$(neat) 1 710 and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 1.00—3.20 (m, 9 H), 2.17 (s, 3 H, Me), 3.42, 3.99 (ABq, *J* 13 Hz, 2 H, CH_2Ph), and 7.38 (s, 5 H, Ph).

Acknowledgements

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