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THE APPLICATION OF THE SULPHIDE CONTRACTION TO THE SYNTHESIS OF SOME SIMPLE PYRROLIDINE ALKALOIDS

RODOLFO GHIRLANDO, ARTHUR S HOWARD*, RUTH B KATZ AND JOSEPH P MICHAEL*

Department of Chemistry, University of the Witwatersrand, Johannesburg, 2000

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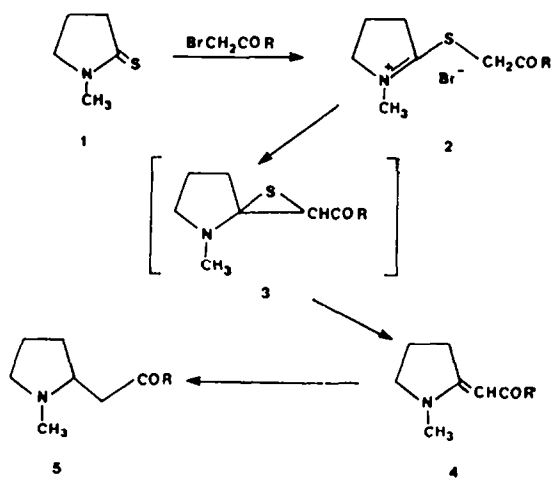
Abstract - The alkaloids (±)-hygrine, (±)-dehydrodarlinine, (±)-dehydrodarlingianine, and (±)-N-methylruspolinone have been synthesised by selective reduction of vinylogous amides formed by sulphide contraction of the salts prepared by reaction of N-methyl-2-thiopyrrolidone with the appropriate bromomethyl ketones.

The formation of a C to C bond by the extrusion of sulphur from the C-S-C linkage has been known for many years[1]. The synthetic potential of this reaction, however, only became generally recognised after the development by Eschenmoser of the sulphide contraction sequence. This was initially used by him in the vitamin B12 work for the synthesis of vinylogous amidines[2] and later extended to include the synthesis of vinylogous amides, vinylogous urethanes and enolisable β-dicarbonyl compounds[3].

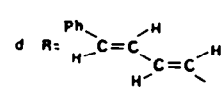
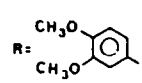
Application of the sulphide contraction to thiolactams results in the extension of the C skeleton at the C atom on which the N is substituted. This is potentially very useful in alkaloid synthesis and has been exploited by us[4] and by other workers[5]. Many simple pyrrolidine alkaloids have structures containing substituents at C2 of the pyrrolidine ring and clearly the sulphide contraction is ideally suited for use in the synthesis of such structures. This is illustrated in the Scheme for (±)-hygrine (5a)[6], (±)-dehydrodarlinine (5c)[7], (±)-dehydrodarlingianine (5d)[7] and (±)-N-methylruspolinone (5e)[8].

The first step of the sequence, formation of the α-thio iminium salt, is reversible and it has been reported that in some cases, in order to obtain good yields it is necessary to use special conditions[9], or a counterion of very low nucleophilicity[10]. In the present cases no problems were experienced and the salt formations went to completion albeit rather slowly.

SCHEME



Series: a R=CH_3; b R=Ph; c R= 

d R=  ; e R= 

The early work on the development of the sulphide contraction was restricted to the use of secondary thioamides and thiolactams and it was reported[3] that the experimental conditions necessary for the contraction step were

strongly dependant on the nature of the group which is attached to sulphur in the first step. In some cases heating with a thiophile alone was sufficient, in others the use of a strong base and a thiophile was necessary while in one case sulphur was spontaneously extruded. Other workers have reported[11] that successful contractions may be achieved by the use of base alone. In addition we[12] and others[9,10] have noted that when tertiary thioamides or thiolactams are used the contraction step proceeds much more rapidly and under very much milder temperature conditions than those found by Eschenmoser to be necessary for the secondary systems. In the present work it was felt that a brief survey of the results obtainable under a variety of conditions was merited. The results are summarised in the Table. It is quite clear that for substrates of this type the best yields are obtained using both a base and a thiophile. In the absence of either reagent, nucleophilic attack at the α-C competes effectively with the sulphide contraction although in the case of the weakly nucleophilic $P(OEt)_3$ the competition is not too severe.

Application of the appropriate conditions results in the conversion of 1 to the vinylogous amides 4a - e in yields of at least 80%. The assignment of the trans-s-cis structures to these compounds rests largely on the positions of absorptions of the methylene protons at C3 in the ring. In secondary vinylogous amides of this type, where the cis-s-cis structure is greatly favoured by the resultant H-bonding, these protons absorb at around 2.7 ppm[3]. In compounds 4a - e they absorb at near 3.2 ppm. It is only in the trans-s-cis isomers, where the methylene protons at C3 fall into the deshielding zone of the carbonyl group that this shift is readily explainable. The assignment of the trans geometry to the double bond in 4a, in addition, supported by the magnitude of the extinction co-efficient in the ultraviolet spectrum[13].

The literature records[14] that the reduction of vinylogous amides to β-aminoketones is problematic, hydrogenolysis of the amino group and further reduction of the carbonyl group being frequently encountered. In our hands erratic results were obtained when attempts were made to reduce 4a or 4b by a variety of catalytic

TABLE

Experiment	Salt	Base	Thiophile	Products
1	2a	K^tOBu	-	4a, 42%[a]; 1,35%[a]
2	2a	Et_3N	-	4a, 45%[b]; 1,48%[b]
3	2b	Et_3N	-	4b, 47%[a]; 1,27%[a]
				$(PhCOCH_2S)_2$; 20%
4	2a	$EtN(^iPr)_2$	-	4a, 49%[b]; 1,43%[a]
5	2a	-	Ph_3P	1,63[a]; $Ph_3P = CHCOCH_3$, 69%[a]
6	2a	-	$P(OEt)_3$	4a, 74%[a]; 1, Present but not isolated in pure form
7	2a	Et_3N	Ph_3P	4a, 90%[b]

a = chromatographically pure

b = distilled

methods[12], but reliably good results were obtained using lithium aluminium hydride. Mass spectra of the total crude products showed no signs of overreduction and chromatographically pure products were obtained in yields of greater than 85%. Further purification by distillation or crystallization gave samples having spectra in full agreement with those in the literature[15].

EXPERIMENTAL

Melting points are uncorrected. All solvents were distilled before use. Acetonitrile was distilled from CaH_2 and stored over 4A molecular sieves. Ether was dried over sodium, while THF was distilled from sodium/benzophenone immediately prior to use. Thin layer chromatograms (TLC's) were run on Merck DC - Fertigplatten Kieselgel F - 254, while column chromatography was performed using Merck Kieselgel 60. Distillations were carried out in a Kugelrhor apparatus. Ultraviolet spectra were run in ethanol and are quoted as λ_{max} (ε_{max}). ^{13}C NMR and PMR spectra were recorded in $CDCl_3$ and absorptions are quoted on the δ scale relative to TMS. High resolution mass spectra (HRMS) were recorded on a Varian MAT 212 mass spectrometer in conjunction with a Varian SS-188 data collection system.

Survey of conditions for the sulphide contraction

The salts (2 in the Scheme) were prepared according to the general procedure below.

Reactants: see Table

Solvent : Acetonitrile in all cases except for experiments 1 (^tBuOH) and 6 ($CHCl_3$)

Time and temperature: Less than 1 h at room temperature except for experiments 5 (reflux 6 h) and 6 (reflux 2 h).

Product isolation: Solvent removed in vacuo. In experiment 1 the residue was chromatographed directly. In all other cases the residue was dissolved in $CHCl_3$ or CH_2Cl_2 and either washed with water to remove amine salts (experiments 2,3 and 4) or extracted with acid (2 M HCl). The basic products were recovered from the acid by basification and extraction with $CHCl_3$. Where necessary further purification by chromatography was carried out.

Preparation of trans, trans-1-bromo-6-phenylhexa-3,5-dien-2-one:

A solution of pyrrolidone hydrotribromide (5.1g, 11 mmol) in 100 ml THF was added dropwise over 2 h to a mixture of 6-phenylhexa-3,5-dien-2-one[16] (1.7g, 10 mmol) and 2-pyrrolidone (0.76 ml, 10 mmol) in 100 ml THF. After stirring at room temperature for a further 2 h, the mixture was filtered and the solvent removed. An ethereal solution of the residue was washed with water. Removal of the solvent yielded 2.9g of crude product. Chromatography on silica gel, eluting with hexane-ether gave the desired product (1.36g, 5.4 mmol) in 54% yield. Recrystallization from ether gave a yellow solid, mp 74 - 75°C (TLC, hexane-ethyl acetate, 1:1, R_f = 0.74) IR (KBr) 650, 695, 760, 1005, 1585, 1675 cm^{-1}; PMR (80 MHz) 4.02 (s, 2, CH_2Br), 6.49 (d, 1, J = 14.8 Hz, COCH), 6.9 - 7.7 ppm (m,8); PMR (500 MHz) 6.45 (d,1, J = 15.3 Hz, H3) 6.87 (dd, 1, J = 15.5, 10.7 Hz, H5) 6.97 (d, 1, J = 15.5 Hz, H6) 7.44 ppm (dd, 1, J = 15.3, 10.7 Hz, H4); ^{13}C NMR (126 MHz) 32.87, 125.40, 126.06, 127.30, 128.74, 129.40, 135.61, 142.86, 145.14, 190.83; MS 252 (7,M^+), 250(8,M^+), 171(50), 157(72), 129(62), 128(100), 127(39), 77(38); HRMS 249.99918 ($C_{12}H_{11}OBr$ requires 249.99941). In addition, 13% of starting material was recovered (216 mg, 1.3 mmol) TLC, R_f = 0.63) and trans, trans-1,1-dibromo-6-phenylhexa-3,5-dien-2-one (362 mg, 1.1 mmol) was obtained in 11% yield. Recrystallization from ether gave this compound as a yellow solid, mp 82 - 83°C (TLC, R_f = 0.85); IR (KBr) 685, 735, 755, 1000, 1175, 1585, 1600, 1645 cm^{-1}; PMR (80 MHz) 5.88 (s, 1, $CHBr_2$), 6.73 - 7.58 ppm (m, 9); MS 332(2,M^+), 330 (3.6,M^+), 328(1.9,M^+), 157(100), 129(35), 128(47), 115(71), 102(25), 77(29); HRMS 331.90590 ($C_{12}H_{10}OBr_2$ requires 331.90600).

General Procedure for Salt formation and Sulphide Contractions:

A slight excess of the requisite bromoketone was added to a solution of N-methyl-2-thiopyrrolidone in a minimum amount of ether or acetone. The salt formations were monitored by TLC, and after 10 - 24 h were found to be complete. The solvent was then removed, and replaced with acetonitrile or dichloromethane. Triphenylphosphine was then added (1 eq),

followed by a slight excess of triethylamine. After 2 h at room temperature any precipitated solid was filtered off, the solvent was removed and the residue subjected to acid-base work-up. The products were generally obtained in a high state of purity as evidenced by TLC.

Preparation of 1-Methyl-2-acetylmethylene-pyrrolidine (4a):

N-Methyl-2-thiopyrrolidone (3.5 mmol) was reacted with bromoacetone according to the general procedure. Compound (4a) was obtained in 90% yield after distillation at 100°C/0.5mm Hg. IR (film) 1535, 1620 cm^{-1}; PMR (60 MHz) 1.88 (s, $COCH_3$) and 1.6 - 2.2 (m, $CH_2CH_2CH_2$) 5 together, 2.78 (s, 3, NCH_3), 3.04 (t, J = 8 Hz, 2, $CH_2C=$), 3.32 (t, J = 8 Hz, 2, NCH_2), 4.77 (s, 1, =CH); ^{13}C NMR (126 MHz) 20.37, 30.00 32.74, 32.80, 53.85, 88.97, 165.35, 193.48; UV 304(26300), + 1 drop 11 M HCl in 3 ml: 291(24500); MS 139(39, M^+), 125(10), 124(100), 96(10), 94(8), 68(15), 67(8), 55(10). The picrate salt was recrystallized from 95 % ethanol, mp 135 - 136.5°C. Found: C, 45.8; H, 4.3; N, 15.2 ($C_{14}H_{16}N_4O_8$ requires: C, 45.7; H, 4.4; N, 15.2%).

Preparation of 1-methyl-2-benzoylmethylene-pyrrolidine (4b):

N-Methyl-2-thiopyrrolidone (0.90 mmol) was reacted with phenacyl bromide according to the general procedure. Compound (4b) was obtained in 90% yield as a chromatographically pure solid (TLC, benzene - methanol, 9:1, R_f = 0.44), which, after recrystallization from petroleum ether 40 - 60°C, melted at 103 - 103.5°C. The weight loss on recrystallization was large. IR (KBr) 1540, 1572, 1585, 1600 cm^{-1}; PMR (60 MHz) 1.7 - 2.3 (m, 2, $CH_2CH_2CH_2$), 2.92, (s, 3, NCH_3) 3.18 - 3.54 (m, 4, NCH_2 and $CH_2C=$), 5.62 (s, 1, =CH), 7.25 - 7.38 (m, 3, aromatic), 7.70 - 7.90 (m, 2, aromatic); ^{13}C NMR (20 MHz) 20.5, 33.1, 33.4, 54.3, 85.9, 126.9, 127.2, 129.9, 141.8, 167.3, 187.1; UV 243(13500), 334(26900), + 1 drop 11 M HCl in 3 ml: 230(7400), 243(5500) 321(28200); MS 201(58, M^+), 200(62), 184(36), 124(100), 105(12), 96(22), 77(25). The picrate salt was recrystallized from 95% ethanol, mp 135.5 - 137°C. Found C, 53.4; H, 4.1; N, 12.7. ($C_{19}H_{18}N_4O_8$ requires: C, 53.0; H, 4.2; N, 13.0%.)

Preparation of trans, trans-1-(1-methyl-2-pyrrolidinylidene)-4-phenylbut-3-ene-2-one (4c):

N-Methyl-2-thiopyrrolidone (10 mmol) was reacted with trans-1-bromo-4-phenylbut-3-ene-2-one[18] according to the general procedure. Compound (4c) was obtained in 80% yield after chromatography on silica gel, with hexane-acetone as eluant, of the crude product obtained after the normal work-up procedure (TLC, ether, R_f = 0.62). Recrystallization from acetone gave an analytical sample of the yellow solid, mp 103 - 104°C; IR ($CHCl_3$) 992, 1125, 1300, 1415, 1480, 1540, 1595 cm^{-1}; PMR (500 MHz) 1.79 (quintet, 2, J = 7.4 Hz, $CH_2CH_2CH_2$), 2.71 (s, 3, NCH_3), 3.19 and 3.21 (2 x t overlapping, 4, J = 6.7 and 7.2 Hz, NCH_2, and $=CCH_2$), 5.02 (s, 1, NC=CH), 6.67 (d, 1, J = 15.6 Hz, COCH=), 7.12 - 7.24 (m, 3, aromatic), 7.39 and 7.34 - 7.45 (d and m overlapping, 3, J = 15.5 Hz, d from ArCH); ^{13}C - NMR (126 MHz) 20.25, 32.83, 33.22, 54.08, 90.33, 127.17, 128.15, 128.31, 129.92, 135.69, 136.33, 166.82, 184.24; UV 288(14800), 296(14500), 364(30800) + 1 drop 11 M HCl in 3 ml: 366 (38300); MS 227(96, M^+), 226(68), 150(37), 136(33), 124(100), 97(39), 77(43), 68(40); Found: C, 78.65; H, 7.63; N, 6.30 ($C_{15}H_{17}NO$ requires: C, 79.26; H, 7.54; N, 6.16%)

Preparation of trans, trans-1-(1-methyl-2-pyrrolidinylidene)-6-phenylhexa-3,5-dien-2-one (4d):

N-Methyl-2-thiopyrrolidone (4.0 mmol) was reacted with trans, trans-1-bromo-6-phenylhexa-3,5-dien-2-one according to the general procedure with the modification that, because of the instability of the bromo compound, the salt formation was performed at 4°C, and hence was much slower, that is, the reaction was only complete after 3 days. Compound (4d) was obtained in 80% yield after the normal work-up procedure (TLC, ether, R_f = 0.60). Recrystallization from acetone gave the product as a yellow solid mp 147 - 149.5°C; IR (KBr) 710, 755, 1000, 1530, 1580 cm^{-1}; PMR (80 MHz) 1.80-2.20 (m, 2, $CH_2CH_2CH_2$, 2.90 (s, 3, NCH_3), 3.35 and 3.43 (2 x t overlapping, J = 7 Hz, 4, NCH_2 and $=CCH_2$), 5.10 (s, 1, C=CHCO), 6.30 (d, 1, J = 15 Hz, COCHCH), 6.73 - 6.90 (m, 2), 6.95 - 7.48 ppm (m, 6), PMR (500 MHz), 6.33 (d, J = 15.0 Hz, 1, H3), 6.78 (d, J = 15.6 Hz, 1, H6),

6.84 (dd, J = 15.5, 10.7 Hz, H5), 7.27 (dd, J = 15.1, 10.5 Hz, H4); ^{13}C NMR (126 MHz) 20.78, 33.27, 33.56, 54.53, 90.69, 126.69, 127.83, 128.07, 128.56, 134.16, 136.86, 137.22, 137.39, 167.06, 185.16; UV 274(6820), 326(21000), 377(34500), + 1 drop 11 M HCl in 3 ml: 266(5220), 394(44800); MS 253(88,M$^+$), 252(65), 162(32) 148(35), 136(100), 134(59), 128(35), 124(76), 97(47); HRMS 253.14633 ($C_{17}H_{19}NO$ requires: 253.14665).

Preparation of 1-methyl-2-veratroylmethylene-pyrrolidine (4e):

N-Methyl-2-thiopyrrolidone (3.7 mmol) was reacted with 3,4-dimethoxyphenylbromomethyl ketone[17] according to the general procedure. Compound (4e) was obtained in 97% yield as a pale yellow solid. An analytically pure sample, mp 135 - 135.5°C, was obtained after recrystallization from acetone (TLC, ether, R_f = 0.13); IR ($CHCl_3$) 1025, 1265, 1535, 1590, 1600, 1615 cm^{-1}; PMR (500 MHz) 1.86 (quintet, 2, J = 7.6 Hz, $CH_2CH_2CH_2$), 2.80 (s, 3, NCH_3) 3.24 (t, 2, J = 7.8 Hz), 3.29 (t, 2, J = 7.3 Hz), 3.76 and 3.80 (2 x s, 6, OCH_3), 5.54 (s, 1, =CH), 6.71 (d, 1, J = 8.3 Hz, aromatic CH), 7.36 (dd, 1, J = 8.3 Hz, 1.9 Hz, aromatic CH), 7.45 ppm (d, 1, J = 1.9 Hz, aromatic CH), ^{13}C NMR (126 MHz) 20.52, 33.03, 33.30, 54.19, 55.55, 55.58, 85.33, 109.66, 110.15, 120.02, 134.69, 148.31, 150.66, 166.89, 185.93; UV 229(13700), 271(6200), 342(28300), + 1 drop 11 M HCl in 3 ml: 236(9270), 278(6800), 354(19600); MS 261(74, M$^+$), 260(73), 246(46), 244(43), 124(100), 96(28), 68(25); Found: C, 69.13; H, 7.76; N, 5.43; ($C_{15}H_{19}NO_3$ requires: C, 68.92; H, 7.33; N, 5.35%).

General Procedure for lithium aluminium hydride reductions:

Equimolar quantities of lithium aluminium hydride and the vinylogous amides were stirred together in dry ether at room temperature for 30 min. (The reaction time, temperature and quanitity of reducing agent were found to be critical for selective reduction.) Water was added dropwise to destroy unreacted hydride; the ether solution was dried over sodium sulphate and then filtered. The solvent was evaporated, yielding the products which were obtained in high purity as judged by TLC.

Preparation of (±)-hygrine (5a)

Compound (4a) (1.22 mmol) was reduced according to the general procedure, giving an 83% yield of hygrine (5a) which on distillation at 85°C, 15 mm Hg (lit[7] 76 - 77°C, 11 mm Hg) gave a 65% yield of an oil having IR, PMR and MS spectra identical to those described in the literature[7]. The picrate salt was recrystallized from 95% ethanol, mp 153.5 - 155°C (lit[7] 149 - 151°C).

Preparation of (±)-1-methyl-2-benzoylmethyl-pyrrolidine (5b):

Compound (4b) (0.54 mmol) was reduced according to the general procedure, giving a 93% yield of reduced product (5b) which was distilled at 165°C, 20 mm Hg (lit[19] 150°C, 3 mm Hg). The distilled yield was 87%. IR (film) 1588, 1675 cm^{-1}; PMR (60 MHz) 2.32 (s, NCH_3) and 1.50 - 3.42 (m) all 12, 7.33 - 7.51 (m, 3, aromatic), 7.80 - 7.97 (m, 2, aromatic); MS 203(17,M$^+$), 126(6), 105(33), 85(21), 84(100), 82(33), 77(47), 70(12). The picrate salt was recrystallized from acetone - dichloromethane, mp 165.5 - 166.5°C. Found: C, 52.7; H, 4.6; N, 13.4. ($C_{19}H_{20}N_4O_8$ requires: C, 52.8; H, 4.7; N, 13.0%).

Preparation of (±)-dehydrodarlinine (5c):

Vinylogous amide (4c) (0.5 mmol) was reduced according to the general procedure, resulting in a 98% yield of dehydrodarlinine as a chromatographically pure yellow oil (TLC, ether, R_f = 0.15). Despite extensive efforts this oil could not be induced to crystallize (lit[7] mp 39 - 40°C), but the IR, PMR and MS spectra of the oil were identical to those obtained by Bick[7,15].

Preparation of (±)-dehydrodarlingianine (5d):

Vinylogous amide (4d) (0.8 mmol) was reduced according to the general procedure resulting in a 91% yield of dehydrodarlingianine as a chromatographically pure solid (TLC, Acetone-methanol, 9:1, R_f = 0.20). Recrystallization from a large volume of pentane gave a solid mp 41 - 44°C (lit[7] 42 - 44°C). The IR, PMR and MS spectra were identical to those obtained by Bick[7,15].

Preparation of (±)-N-methylruspolinone (5e):

Vinylogous amide (4e) (0,5 mmol) was reduced according to the general procedure, excepting that dry THF was used in place of ether, owing to the insolubility of (5e)in ether. The product was obtained in 92% yield as a chromatographically pure yellow oil (TLC, ether, R_f = 0.04). The PMR, ^{13}C NMR and MS data obtained for this compound were found to be identical to those quoted in the literature[8b]

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