SYNTHESIS OF PYRROLIZIDINES AND RELATED COMPOUNDS BY ALDOL CYCLIZATION OF N-[α-(METHYLTHIO)ACETYL]-α-AMINOALDEHYDES

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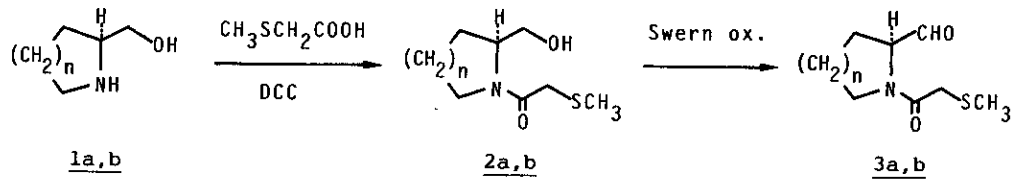
Abstract- Treatment of 1-[α-(methylthio)acetyl]-2-pyrrolidinecarbaldehyde with sodium hydride in tetrahydrofuran (THF) gave the aldol condensation product, 5,6,7,7a-tetrahydro-2-methylthio-3H-pyrrolizin-3-one. However, when the same aldehyde was treated with sodium hydroxide in aqueous THF, 5,6,7,7a-tetrahydro-7a-hydroxy-3-methylthio-3H-pyrrolizin-3-one was obtained. These reactions were applied to the synthesis of indolizidine and pyrrolo[1,2-a]indole derivatives.

Alkaloids containing the pyrrolizidine, indolizidine, and pyrrolo[1,2-a]indole ring systems have been widely found in plants. Some of these alkaloids demonstrate a broad range of physiological activities and have generated substantial synthetic interest.[1-3] In connection with our synthetic program to develop new methods for alkaloid synthesis utilizing organo-sulfur compounds,[4,5] our attention has been focussed on the use of sulfur-substituted carbanion to construct the pyrrolidine ring of these alkaloids. The present paper describes results of our work on an aldol cyclization of some N-[α-(methylthio)acetyl]-α-aminoaldehydes.

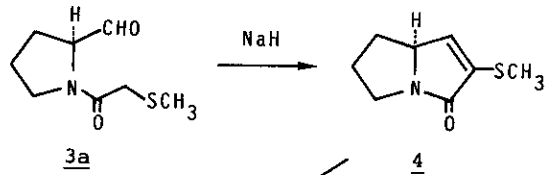
The aldehydes **3a,b** were prepared by N-acylation of the amino alcohols **1a,b** with methylthioglycolic acid in the presence of N,N'-dicyclohexylcarbodiimide (DCC) followed by Swern oxidation[6] of the resulting alcohols **2a,b**.

Treatment of the aldehyde **3a** with 2.4 molar equivalents of sodium hydride in tetrahydrofuran (THF) under a nitrogen atmosphere at room temperature for 2 h gave 5,6,7,7a-tetrahydro-2-methylthio-3H-pyrrolizin-3-one (**4**) in 46% yield. The ^{1}H nmr spectrum of **4** exhibited a vinylic proton signal at δ 6.55 as a doublet (J=2 Hz)

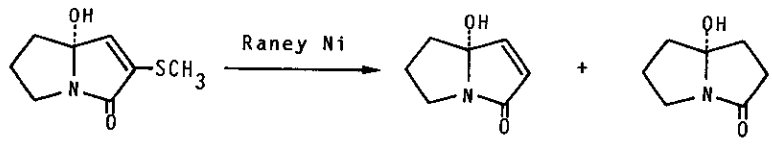


1a,b 2a,b 3a,b

a: n=1, b: n=2



3a 4



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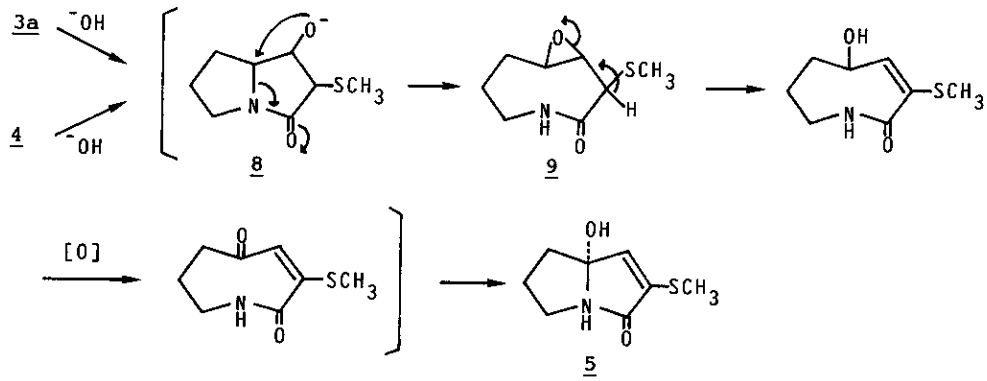


8 9 5

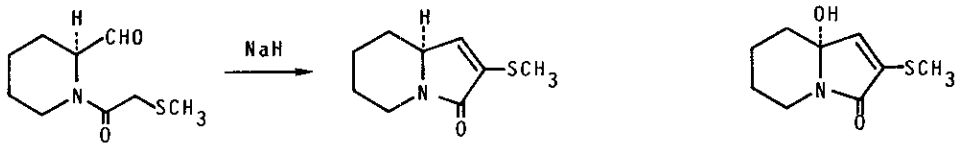
and its ir spectrum showed absorptions at 1685 (NC=O) and 1575 (C=C) cm^{-1}. The formation of the lactam **4** from **3a** can be well rationalized in terms of a usual intramolecular aldol condensation. However, the base treatment of **3a** in the presence of water was found to give an abnormal aldol cyclization product. Thus, on treatment with sodium hydride in the presence of one drop of water under a nitrogen atmosphere, the aldehyde **3a** afforded the hydroxy-lactam **5** as a major product along with the compound **4**. The structure of **5** was assigned on the basis of the following spectral and chemical evidence. The ir spectrum showed hydroxyl

absorptions at 3580 and 3380 cm^{-1} together with absorptions at 1700 (NC=O) and 1580 (C=C) cm^{-1}. The ^{1}H nmr spectrum (300 MHz) exhibited a vinylic proton signal at δ 6.24 as a singlet. The ^{13}C nmr spectrum (75 MHz) showed three singlets at δ 97.29 (C-7a), 138.55 (C-2), and 170.90 (C-3), and one doublet at δ 134.90 (C-1). Reduction of the compound **5** with Raney nickel in boiling acetone gave an unsaturated hydroxy-lactam **6** (31%) together with the saturated lactam **7** (34%). Similar reduction of **5** in boiling methanol afforded only the saturated lactam **7** in 88% yield.

In order to obtain some informations on the mechanism for the formation of the abnormal product **5** from **3a**, we treated the lactam **4** with sodium hydroxide in aqueous THF, whereupon the hydroxy-lactam **5** was again obtained. On the other hand, after exposure of the THF solution to water or oxygen gas in the absence of base at room temperature for 2 h, the lactam **4** was recovered unchanged. Treatment of **3a** with sodium hydride under an oxygen atmosphere gave a complex mixture of products.

Although few mechanistic details for the formation of **5** from **3a** or **4** are available at the moment, one possible explanation would involve an epoxide intermediate **9** which is formed by an intramolecular displacement reaction of the aldol intermediate **8**. This epoxide **9** may undergo sequential ring opening, oxidation, and transannular cyclization to lead to **5**.[7]

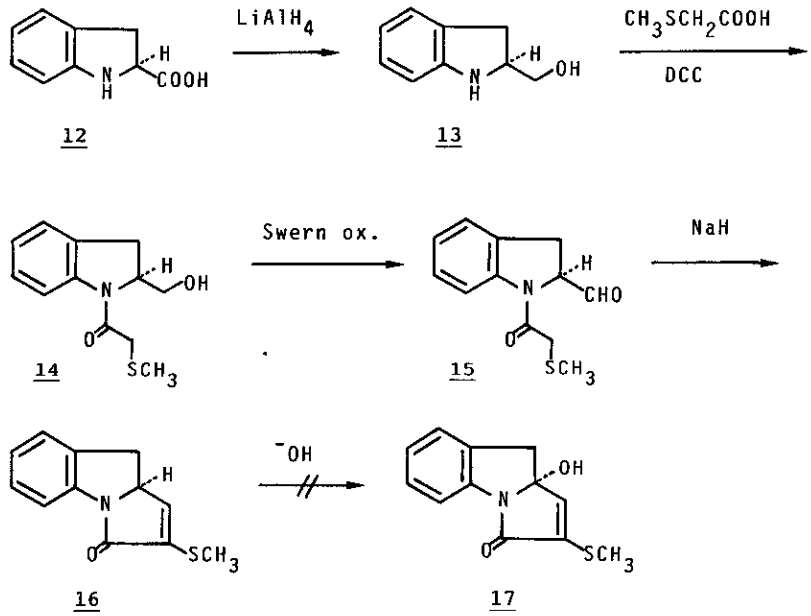
The same behavior was observed with the aldehyde **3b**. On treatment with sodium hydride in dry THF, the aldehyde **3b** gave the indolizidine derivative **10** in 55% yield, while in the presence of one drop of water, **3b** afforded a 1:1 mixture of the hydroxy-lactam **11** and **10**.



3b 10 11

Finally, we examined the cyclization of the aldehyde **15**, which was prepared from 2,3-dihydro-1H-2-indolemethanol (**13**) by a similar sequence of the reactions employed for the preparation of **3a,b**. Treatment of **15** with an equimolar amount of sodium hydride in dry THF at room temperature for 2 h gave the expected lactam **16** in 43% yield as yellow crystals. The ^{1}H nmr spectrum exhibited a broad singlet

due to the proton on C-1 at δ 6.24 and a doublet of doublets due to the proton on C-9a at δ 3.96 (J=8, 4 Hz). However, the base treatment of the aldehyde **15** or the lactam **16** in the presence of water gave no hydroxylated lactam **17**.



We are currently investigating the application of this methodology and the transformation of the products thus obtained into useful molecules.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded with a JASCO IRA-1 spectrophotometer in $CHCl_3$ unless otherwise stated. ^1H Nmr and ^{13}C nmr spectra were determined with a JEOL JNM-PMX 60 spectrometer (60 MHz for ^1H) or a Varian XL-300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C) in $CDCl_3$ using tetramethylsilane as an internal standard. Low- and high resolution mass spectra (ms) were obtained with a Hitachi M-80 instrument at 20 eV. Column chromatography was performed on silica gel 60 PF_{254} (Merck) for preparative tlc under pressure.

1-[α-(Methylthio)acetyl]-2-pyrrolidinemethanol (2a).

To a solution of (S)-(+)-2-pyrrolidinemethanol (**1a**)(1.1 g, 10.6 mmol) and methyl-

thioglycolic acid (1.2 g, 11.6 mmol) in dichloromethane (30 ml) was added a solution of N,N'-dicyclohexylcarbodiimide (DCC)(2.4 g, 11.6 mmol) in dichloromethane (10 ml), and the mixture was stirred at room temperature for 24 h. The precipitated urea was removed by filtration and the filtrate was washed with saturated aqueous $NaHCO_3$ solution, then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (ethyl acetate) to give the amide **2a** (1.5 g, 73%) as a pale yellow oil; ir (ν, cm^{-1}, neat): 3380 (OH), 1620 (C=O); ^1H nmr (δ, ppm, 60 MHz): 1.5-2.2 (4H, m), 2.20 (3H, s, SMe), 3.23 (2H, s, $COCH_2$), 3.43-3.90 (4H, m), 3.9-4.4 (1H, m, NCH), 4.73 (1H, br, OH). Anal. Calcd for $C_8H_{15}NO_2S$: C, 50.77; H, 7.99; N, 7.40. Found: C, 50.61; H, 8.00; N, 7.30.

1-[α-(Methylthio)acetyl]-2-piperidinemethanol (2b).

According to the procedure as described above for the preparation of **2a**, the amide **2b** was synthesized from (±)-2-piperidinemethanol (**1b**)(5.0 g, 43.4 mmol), methylthioglycolic acid (5.1 g, 47.8 mmol), and DCC (9.9 g, 47.8 mmol) in 13% yield (1.1 g) as an yellow oil; ir (ν, cm^{-1}): 3390 (OH), 1615 (C=O); ^1H nmr (δ, ppm, 60 MHz): 1.4-2.0 (6H, m), 2.16 (3H, s, SMe), 2.5-3.0 (1H, br), 3.1-5.0 (5H, m), 3.30 (2H, s, $COCH_2$). Anal. Calcd for $C_9H_{17}NO_2S$: C, 53.17; H, 8.43; N, 6.89. Found. C, 52.87; H, 8.50; N, 6.79.

1-[α-(Methylthio)acetyl]-2-pyrrolidinecarbaldehyde (3a).

A solution of oxalyl chloride (1.56 ml, 17.9 mmol) in dry dichloromethane (6 ml) was cooled to -60°C and a solution of dimethylsulfoxide (2.69 ml, 37.9 mmol) in dry dichloromethane (6 ml) was added dropwise over the period of 10 min. After completion of addition, a solution of the alcohol **2a** (3.0 g, 15.8 mmol) in dry dichloromethane (6 ml) was added by portions and the mixture was stirred for 15 min. Triethylamine (11 ml, 79 mmol) was added and the mixture was allowed to warm to room temperature. Water (10 ml) was added and the mixture was stirred for 10 min. The organic layer was separated and the aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (ethyl acetate) to give the aldehyde **3a** (2.0 g, 68%) as an yellow oil; $[\alpha]_D$ -81.3° (c 1.45, EtOH);[8] ir (ν, cm^{-1}): 1730 (CHO), 1630 (NC=O); ^1H nmr (δ, ppm, 60 MHz): 1.5-2.2 (4H, m), 2.20 (3H, s, SMe), 3.23 (2H, s, $COCH_2$), 3.31-3.90 (2H, m), 4.1-

4.7 (1H, m, NCH), 9.48 (1H, d, J=2 Hz, CHO). Exact ms calcd for $C_8H_{13}NO_2S$: 187.0666. Found: 187.0671.

1-[α-(Methylthio)acetyl]-2-piperidinecarbaldehyde (3b).

According to the procedure as described above for the preparation of **3a**, the aldehyde **3b** was obtained from the alcohol **2b** (1.1 g, 5.5 mmol) in 47% yield (0.5 g) as an yellow oil; ir (ν, cm^{-1}): 1720 (CHO), 1630 (NC=O); ^1H nmr (δ, ppm, 60 MHz): 1.3-2.0 (6H, m), 2.16 (3H, s, SMe), 3.1-5.3 (3H, m), 3.36 (2H, s, $COCH_2$), 9.23 (1H, m, CHO). Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.71; H, 7.51; N, 6.96. Found: C, 53.40; H, 7.51; N, 6.90.

5,6,7,7a-Tetrahydro-2-methylthio-3H-pyrrolizin-3-one (4).

To a suspension of sodium hydride (60% mineral oil dispersion)(413 mg, 10.3 mmol), which was washed three times with dry n-hexane, in dry THF (10 ml) was added a solution of the aldehyde **3a** (800 mg, 4.3 mmol) in dry THF (10 ml) at 0°C and the mixture was stirred at room temperature for 2 h. Water (1 ml) was added to the reaction mixture and the whole was neutralized with 10% HCl, then extracted with dichloromethane. The extract was dried over $MgSO_4$, the solvent was removed by evaporation, and the residue was chromatographed on silica gel (ethyl acetate) to give tha lactam **4** (340 mg, 46%) as colorless crystals; $[\alpha]_D$ -0.6° (c 1.64, EtOH);[8] mp 120-121°C (from n-hexane-ethyl acetate); ir (ν, cm^{-1}): 1685 (C=O), 1575 (C=C); ^1H nmr (δ, ppm, 60 MHz): 1.9-2.6 (4H, m), 2.35 (3H, s, SMe), 3.2-3.8 (2H, m), 4.0-4.5 (1H, m), 6.55 (1H, d, J=2 Hz, CH=C). Anal. Calcd for $C_8H_{11}NOS \cdot 1/4H_2O$: C, 55.30; H, 6.67; N, 8.06. Found: C, 55.49; H, 6.50; N, 7.82; ms (m/z): 169 (M^+).

5,6,7-7a-Tetrahydro-7a-hydroxy-2-methylthio-3H-pyrrolizin-3-one (5).

(a) From the aldehyde **3a**. To a suspension of sodium hydride (60% mineral oil dispersion)(40 mg, 1.6 mmol) in THF (5 ml) was added succesively one drop of water and a solution of the aldehyde **3a** (270 mg, 1.6 mmol) in THF (5 ml), and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water (1 ml) and the whole was neutralized with 10% HCl and extracted with dichloromethane, then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (ethyl acetate). The first eluate gave the hydroxy-lactam **5** (52 mg, 18%); $[\alpha]_D$ 0° (c 0.83, EtOH); mp 170-171°C (from benzene-n-hexane); ir (ν, cm^{-1}): 3580 (OH), 3380 (OH), 1700 (C=O), 1580 (C=C); ^1H

nmr (δ, ppm, 300 MHz): 1.53 (1H, td, J=12.4, 8.3 Hz, H-7), 2.12 (1H, ddd, J=12.4, 6.8, 1.5 Hz, H-7), 2.19-2.32 (1H, m, H-6), 2.34 (3H, s, SMe), 2.48-2.65 (1H, m, H-6), 3.33 (1H, ddd, J=11.4, 8.3, 2.9 Hz, H-5),3.45 (1H, td, J=11.5, 8.8 Hz, H-5), 3.61 (1H, br, OH), 6.42 (1H, s, H-1); ^{13}C nmr (δ, ppm, 75 MHz): 14.03 (q, SMe), 28.17 (t, C-6), 34.61 (t, C-7), 41.99 (t, C-5), 97.29 (s, C-7a), 134.90 (d, C-1), 138.55 (s, C-2), 170.90 (s, C-3); ms (m/z): 185 (M^+, 100%), 168 (M-OH, 25), 138 (M-SMe, 32). Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.86; H, 6.00; N, 7.56. Found: C, 51.91; H, 5.78; N, 7.38. The second eluate gave the lactam **4** (25 mg, 9%).

(b) From the lactam **4**. To a solution of the lactam **4** (25 mg, 0.15 mmol) was added 10% NaOH solution (1 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was neutralized with 10% HCl and extracted with dichloromethane, then dried over $MgSO_4$. The solvent was evaporated off and the residue (26 mg) was subjected to ^{1}H nmr spectral analysis ($CDCl_3$), which showed the product to be a mixture of the compounds **4** and **5** in a ratio of 4:3.

Reduction of 5 with Raney Nickel.

(a) In acetone. Raney nickel (W-2) (ca. 2 g) was added to acetone (10 ml) and the mixture was heated under reflux for 1 h. To this mixture was added a solution of **5a** (98.1 mg, 5.3 mmol) in acetone (1 ml) and the whole was heated again under reflux for 20 min. The Raney nickel was removed by filtration, the filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (ethyl acetate). The first eluate gave **5,6,7,7a-tetrahydro-7a-hydroxy-3H-pyrrolizin-3-one (6)**(40.3 mg, 31%) as a colorless oil; ir (ν, cm^{-1}): 3570 (OH), 3350 (OH), 1690 (C=O), 1585 (C=C); ^{1}H nmr (δ, ppm, 60 MHz): 1.76-2.76 (4H, m), 3.23-3.83 (3H, m, NCH_2, OH), 5.80 (1H, d, J=6 Hz, COCH=C), 6.96 (1H, d, J=6 Hz, COC=CH). Exact ms calcd for $C_7H_9NO_2$: 139.0633. Found: 139.0659. The second eluate gave **hexahydro-7a-hydroxy-3H-pyrrolizin-3-one (7)**[9](44.6 mg, 34%) as a colorless oil; ir (ν, cm^{-1}): 3580 (OH), 3380 (OH), 1705 (C=O); ^{1}H nmr (δ, ppm, 60 MHz): 1.5-2.5 (6H, m), 3.0-3.9 (5H, m); ms (m/z): 141 (M^+).

(b) In methanol. To a suspension of Raney nickel (W-2) (ca. 2 g) in methanol (10 ml) was added a solution of **5** (101.6 mg, 0.55 mmol) in methanol (1 ml) and the mixture was heated under reflux for 1 h. The Raney nickel was removed by filtration, the filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (ethyl acetate) to give the lactam **7** (68.4 mg, 88%).

3,5,6,7,8,8a-Hexahydro-2-(methylthio)indolizin-3-one (10).

According to the procedure as described above for the preparation of **4**, the lactam **10** was obtained from the aldehyde **3b** (180 mg, 0.89 mmol) in 55% yield (90 mg) as colorless crystals; mp 95-96°C (from petroleum ether); ir (ν, cm^{-1}): 1675 (C=O), 1580 (C=C); ^1H nmr (δ, ppm, 60 MHz): 0.8-2.2 (6H, m), 2.38 (3H, s, SMe), 2.5-3.1 (1H, m, NCH), 3.7-4.5 (2H, m, NCH_2), 6.35 (1H, d, J=2 Hz, CH=C). Exact ms calcd for $C_9H_{13}NOS$: 183.0717. Found: 183.0717.

3,5,6,7,8,8a-Hexahydro-8a-hydroxy-2-(methylthio)indolizin-3-one (11).

To a suspension of sodium hydride (60% mineral oil dispersion) (116.3 mg, 2.9 mmol) in THF (10 ml) was added succesively one drop of water and a solution of the aldehyde **3b** (292.6 mg, 1.5 mmol), and the mixture was stirred at room temperature for 48 h. The solvent was removed by evaporation and the residue was poured into water (10 ml). The whole was neutralized with 10% HCl, and extracted with dichloromethane, then dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene-ethyl acetate=2:1). The first eluate gave the compound **10** (76 mg, 29%). The second eluate gave **3,5,6,7,8,8a-hexahydro-8a-hydroxy-2-(methylthio)indolizin-3-one (11)** (85 mg, 29%) as colorless crystals; mp 196-197°C (from benzene); ir (ν, cm^{-1}, KBr): 3360 (OH), 1670 (C=O), 1575 (C=C); ^1H nmr (δ, ppm, 60 MHz): 1.3-2.1 (6H, m), 2.40 (3H, s, SMe), 3.0-3.5 (2H, m), 3.8-4.2 (1H, m, OH), 6.42 (1H, s, CH=C). Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.57; H, 7.02. Found: C, 54.51; H, 6.70; N, 7.24.

2,3-Dihydro-1*H*-2-indolemethanol (13).

(*S*)-(-)-2,3-Dihydro-1*H*-2-indolecarboxylic acid (**12**) (3.26 g, 20 mmol) in dry THF (30 ml) was added by portions to a suspension of lithium aluminum hydride (759 mg, 20 mmol) in dry THF (30 ml) and the mixture was heated under reflux for 2 h. The complexes thus formed were decomposed with a minimum amount of water and the resulting salts were removed by filtration. The filtrate was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (ethyl acetate-*n*-hexane=1:1) to give the alcohol **13** (1.46 g, 52%) as colorless crystals; mp 66-66.5°C (ethyl acetate-*n*-hexane); ir (ν, cm^{-1}): 3370 (OH); ^1H nmr (δ, ppm, 60 MHz): 2.46-4.30 (7H, m), 6.46-7.26 (4H, m, arom). Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.31; H, 7.42; N, 9.46.

2,3-Dihydro-1-[α-(methylthio)acetyl]-1H-2-indolemethanol (14).

According to the procedure as described for the preparation of **2a**, this compound was synthesized from the alcohol **13** (1.5 g, 10.1 mmol), methylthioglycolic acid (1.2 g, 11.1 mmol), and DCC (2.3 g, 11.1 mmol) in 81% yield (1.9 g) after chromatography on silica gel (ethyl acetate-n-hexane=1:1); ir (ν, cm^{-1}): 3380 (OH), 1640 (C=O); ^1H nmr (δ, ppm, 60 MHz): 2.30 (3H, s, SMe), 2.45-4.30 (7H, m), 4.5-5.0 (1H, m, OH), 6.5-7.3 (4H, m, arom.); mp 91.0-91.5°C (from n-hexane-ethyl acetate). Exact ms calcd for $C_{12}H_{15}NO_2S$: 237.0822. Found: 237.0822.

2,3-Dihydro-1-[α-(methylthio)acetyl]-1H-2-indolecarbaldehyde (15).

According to the procedure as described above for the preparation of **3a**, the alcohol **14** (1.4 g, 6 mmol) was oxidized under the Swern's conditions to give the aldehyde **15** (820 mg, 59%) as an yellow oil after chromatography on silica gel (ethyl acetate-n-hexane=1:1); ir (ν, cm^{-1}): 1720 (CHO), 1645 (NC=O); ^1H nmr (δ, ppm, 60 MHz): 2.15 (3H, s, SMe), 2.8-3.8 (4H, m), 4.9-5.3 (1H, m, NCH), 6.7-7.6 (3H, m, arom.), 7.8-8.3 (1H, m, arom.). 9.56 (1H, d, J=2 Hz, CHO). Exact ms calcd for $C_{12}H_{13}NO_2S$: 235.0666. Found: 235.0688.

9,9a-Dihydro-2-methylthio-3H-pyrrolo[1,2-a]indol-3-one (16).

To a suspension of sodium hydride (30 mg, 0.74 mmol) in dry THF (5 ml) was added a solution of the aldehyde **15** (175 mg, 0.74 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was poured into water (1 ml) and neutralized with 10% HCl, then extracted with dichloromethane. The extract was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (ethyl acetate-n-hexane=1:4) to give the compound **16** as yellow crystals; mp 61-61.5°C (from n-hexane); ir (ν, cm^{-1}): 1720 (C=O), 1590 (C=C); ^1H nmr (δ, ppm, 60 MHz): 2.27 (3H, s, SMe), 3.00 (1H, ddd, J=17, 4, 2 Hz, H-9), 3.60 (1H, ddd, J=17, 8, 2 Hz, H-9), 3.96 (1H, dd, J=8, 4 Hz, H-9a), 6.24 (1H, br s, H-1), 7.0-7.7 (3H, m, arom.), 7.9-8.2 (1H, m, arom.). Anal. Calcd for $C_{12}H_{11}NOS$: C, 66.33; H, 5.10; N, 6.45. Found: C, 66.17; H, 5.09; N, 6.43.

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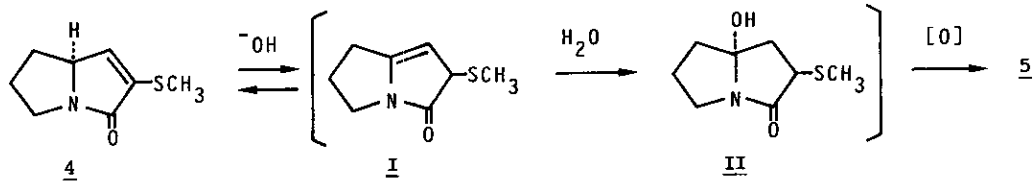
7. An alternative but more speculative one would involve the acyl-enamide intermediate I which may arise from the compound **4** under basic conditions. This intermediate I may undergo hydrolysis followed by oxidation of the resulting lactam II to give the unsaturated hydroxy-lactam **5**. In any event,

it is evident that the formation of **5** from **3a** or **4** involves the oxidation step. Unfortunately, attempts to isolate any postulated intermediates were unsuccessful.



4 I II

8. Optical yield was not determined.

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