A simple and convenient method for the synthesis of 1-dialkyl-aminocarbothioic acid S-[(2,3-epithio)propyl] esters†

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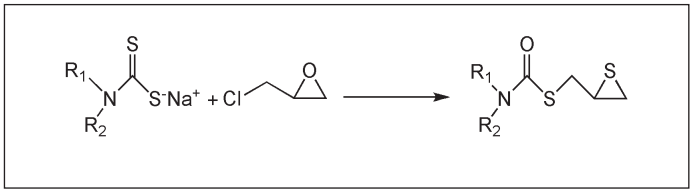

A simple and convenient method for the synthesis of 1-dialkylaminocarbothioic acid S-[(2,3-epithio)propyl] ester was developed by the reaction of 1-dialkylaminocarbodithioic acid-sodium salt with 1-chloro-2,3-epoxypropane in water-methanol mixture at room temperature. An intermediate was isolated and characterized, based on which a possible mechanism was proposed.

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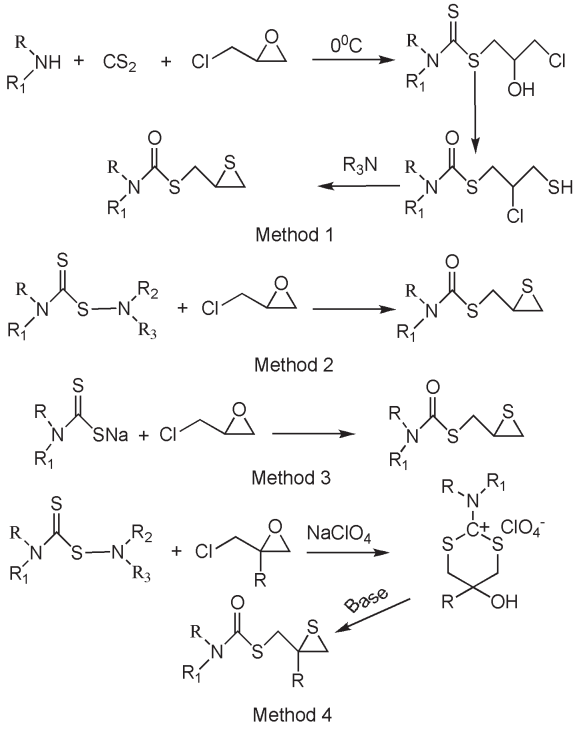
Introduction.

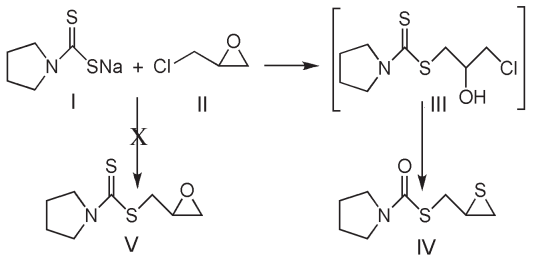
Dialkylaminocarbothioic acid S-[(2,3-epithio)propyl] esters are valuable class of intermediates leading to compounds having herbicidal activity [1-6]. These types of compounds also find their use as additives for synthetic and natural lubricants [7]. The reported procedures for the synthesis of these intermediates involve multi-step reactions, usage of hazardous chemicals, poor yields and heating under vacuum, which is not feasible at industrial level. As in Scheme 1, the reported procedure [5,7] for the synthesis of these intermediates describes two general methods (1 and 2), first a three-step process with isolation of intermediates and the other essentially a single step process. Above two methods give similar yields, but the second step of method 1 involves heating under vacuum, which is not feasible for large-scale synthesis. Whereas, some cases like morpholine, dicyclohexylamine or isopropyl-cyclohexylamine the method 2 is the only successful route with poor yields. Method 3 (Scheme 1) involves reaction in methanol-toluene [7]/benzene [8] at 50 °C, which gave poor yields (45 and 40%) may be due to exothermicity observed during the reaction. Also the usage of benzene as solvent is not desirable. Method 4 [9] (Scheme 1) involves a two-step process using sodium perchlorate where the isolation of intermediate salt is not desirable for large-scale synthesis. Moreover, the purification of these compounds by vacuum distillation is also not preferable as thermal decomposition might occur by loss of sulphur [1,7]. Thus formed allylic product may undergo many side reactions. So, to overcome several drawbacks like low yields, stringent reaction conditions and difficult purification process, there is a need to develop a simple process for the synthesis of 1-dialkylaminocarbothioic acid S-[(2,3-epithio)propyl] ester such that the product

Scheme 1



obtained is pure enough to be used in the next step without further purification. A simple and convenient method for the synthesis of dialkylaminocarbothioic acid S-[(2,3-epithio)propyl] esters is being reported here keeping in view the requirement of an industrial process [10]. The reaction of epichlorohydrin with dialkylaminocarbodithioic acid sodium salt (Scheme 2) should give the corresponding epoxy compound (V) or the thiirane (IV). In our

Scheme 2



experiments thiirane (IV) was the only product isolated. A probable mechanism for thiirane formation has been proposed which has not been previously attempted.

Results and Discussion.

Pyrrolidinecarbodithioic acid sodium salt was reacted with 1-chloro-2,3-epoxypropane in methanol at room temperature (Scheme 2). The reaction mixture showed the formation of an intermediate (III), which later transformed into the product (IV). This conversion remained incomplete even after 96 hours and heating of the reaction created more side products. Therefore, to search for a better solvent for this preparation, the reactions were carried out with different solvents and at temperatures ranging from –10 °C to room temperature (31-36 °C) and higher. The yield and purity of the final product obtained in each experiment is given in Table 1.

The results suggested that the solvent should be protic and polar. The product obtained in methanol did not have the desired purity. The separation of intermediate in water prolonged the reaction. In hexane the yield obtained is much less whereas in dichloromethane the reaction was prolonged due to poor solubility of the dithio salt (I). In dioxane the duration of the reaction is longer which might be due to the absence of a proton and at reflux temperature many side products were formed. Similar result is observed in the reaction where one of the reactant 1-chloro-2,3-epoxypropane (II) was taken as solvent, it may be due to the poor solubility of dithio salt (I) and lack of a proton. It is observed that in all the solvents, except water both the formation of intermediate (III) and its conversion to final product (IV) was occurring simultaneously and this might lead to the formation of side products at longer time periods.

Therefore, it was thought worthwhile to carry out the reaction in such a way that the two steps are done one after the other. The reaction is started in water and after the separation of intermediate (III) methanol is added to make the reaction mixture homogeneous. The reaction was completed in 48 hours. This reaction is further verified with various 1-dialkylaminocarbodithioic acid sodium salts

Table 1

Standardization of Solvent in the Synthesis of Compound IV

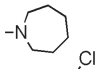
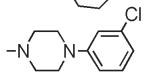
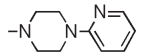
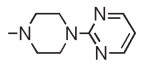
S. No	Solvent	Temperature	Time (h)	Yield [a] (%)	HPLC Purity [b]
1	Methanol	-10 °C to rt	72	84	63
2	Hexane	-10 °C to rt	72	59	66
3	Dichloromethane	-10 °C to rt	120	64	[c]
4	Water	0 °C to rt	120	64	83
5	Dioxane	10 °C to reflux	6 [d]	85	81
6	Epichlorohydrin	-10 °C to rt	72	78	70
7	Methanol + Water	0 °C to rt	48	83	98

[a] crude, [b] column-RP-18 shimpack CLC-ODS(m) 25 cm long; 4.6 mm (ID); Eluent- MeOH/Water (4:1) Isocratic; Flow rate: 0.5ml/min; detection by UV method, [c] many components, [d] at reflux.

(Table 2). This method has a definite advantage over the method 3 [7] of Scheme 1 since no rise in temperature was observed during the reaction and the yields obtained here are high. The utilization of two solvents, water followed by methanol, served the purpose without rise in temperature and was the key to yield enhancement.

Table 2

Yields of the Various 1-Dialkylaminocarbothioic Acid S-[(2,3-epithio)propyl] Esters

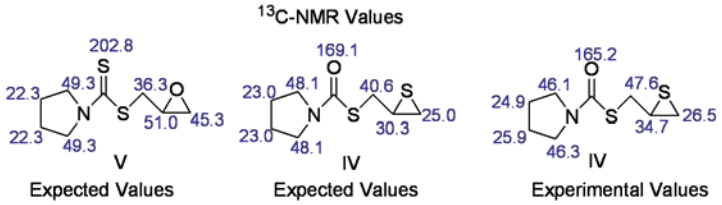
Compound No.	NRR_1	Time (hr)	Yield (%)
1[a]		48	83
2[b]		50	68
3[b]		53	79
4		72	72
5		74	59
6		96	66
7		96	78
8		72	78
9[c]		72	96

[a] ref -[7] and ref -[9], [b] ref -[1], [c] ref -[9]

The reaction of dithio salt (I) with 1-chloro-2,3-epoxypropane (II) gave the unusual compound (IV) instead of the expected compound (V). The formation of compound V is reported [11] only once, but from different reactants, in which supporting data is not provided. So in order to prove that the compounds formed are thiiranes, expected ^{13}C-NMR shifts of both compounds IV and V are

taken using ChemDraw Ultra 7.0 software and compared with experimental values of the synthesized compounds. The experiment values coincide well with the expected values of compound IV (Scheme 3). Attempts were made to isolate and characterize the intermediate III to understand the mechanism of rearrangement. Even though, this intermediate was reported to be unstable [2] we were able to isolate and characterize (data given) it.

Scheme 3



As given in Scheme 4, the mechanism may be proposed on the basis of the conversion of oxiranes to thiiranes [12], the intermediates isolated in earlier work [2-7] and III isolated here. The dithiocarbamate salt (**I**) participates in the epoxide ring opening to give the intermediate (**III**) at –10°C to 0°C, which has been isolated. When compound **III** is allowed to attain room temperature (31-36 °C) it undergoes intramolecular rearrangement to provide the final epithio product (**IV**) *via* a five membered intermediate. In order to check the validity of the proposed mechanism, the intermediate obtained is immediately acetylated (data given) so that further formation of product IV is ceased. It was observed that the acetylated product when stirred in methanol at room temperature for 24 hours and also at reflux for 24 hours, product IV (Scheme 2) was not formed. The above observations help to support the mechanism of the reaction as given in Scheme 4.

Conclusion.

In conclusion, a simple and convenient method for the synthesis of 1-dialkylaminocarbothioic acid S-[(2,3-epithio)propyl] esters has been developed, which offers high yields, mild conditions and high purity.

EXPERIMENTAL

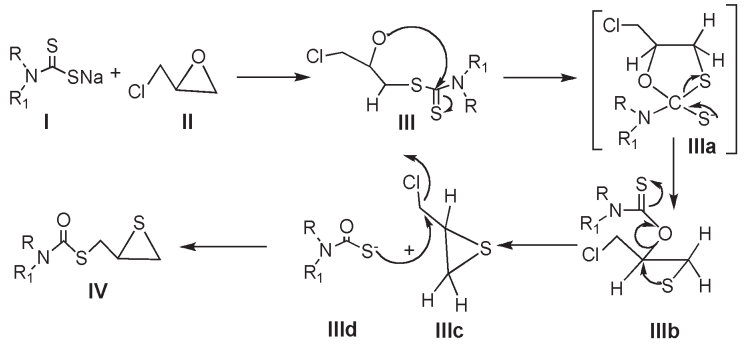
General.

Melting points were determined in open capillary tubes on an electrically heated block and are uncorrected. IR spectra (ν_{max} in cm^{-1}) of the compounds were recorded on a Perkin Elmer FTIR 8201 PC spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-200 FT spectrometer in deuterated solvents with TMS as internal reference (chemical shifts in δ ppm, J in Hz.). Mass spectra were recorded on Jeol/SX-102/DA-6000 FABMS spectrometer. Elemental analyses were performed on Carlo Erba EA-1108 micro analyzer. All compounds were analyzed for C, H and N and the results obtained were within ±0.4% of calculated values. Thin layer chromatography was performed on precoated alumina plastic plates (Aldrich). Anhydrous sodium sulfate was used as drying agent. Expected ^{13}C NMR values were taken from ChemDraw Ultra version 7.0 software. HPLC was done using column-RP-18 shimpack CLC-ODS(m) 25cm long; 4.6mm (ID); Eluent- MeOH/Water (4:1) Isocratic; Flow rate : 0.5ml/minute; detection by UV method.

Standardization of the Solvent in the Synthesis of compound **IV**—General Procedure (Table 1).

A mixture of pyrrolidinecarbodithioic acid sodium salt (I, 2-6 mmol) and appropriate solvent was cooled to required temperature for 30 minutes. Epichlorohydrin (1.5 equivalent; precooled) was added dropwise and the reaction mixture was stirred for the specified time. After completion of the reaction (as monitored by TLC), the reaction mixture was filtered if necessary and then concentrated under reduced pressure in a rotavapor at 35-40 °C. The residue was taken into EtOAc (20 ml), washed with water (5

Scheme 4



ml × 3) and dried (anhydrous Na_2SO_4). The Na_2SO_4 was filtered off and washed with EtOAc (5 ml × 2). The combined filtrate was concentrated as above, gave the product pyrrolidinecarbothioic acid S-[(2,3-epithio)propyl] ester (IV), which was checked for purity by HPLC.

Reaction of Various Dialkylaminocarbodithioic Acid Sodium Salts with Epichlorohydrin—General Procedure (Table 2).

A solution of substituted aminocarbodithioic acid sodium salt (3 mmol) in water (10 ml) was cooled in an ice bath, (0-5 °C) for 15-30 minutes. Epichlorohydrin (1.5 equivalent) was added dropwise with stirring. The reaction mixture became turbid within 2–5 minutes. The stirring was continued in icebath for 30 minutes. Methanol (5 ml) was added and the reaction mixture was slowly brought to room temperature (31–36 °C). The reaction mixture was further stirred at room temperature for the specified time till the completion of the reaction (as monitored by TLC). The reaction mixture was concentrated under reduced pressure in a roto-evaporator to about 5 ml volume and then extracted with EtOAc (10 ml × 3). The combined organic layer was washed with water (5 ml × 4) and dried (anhydrous Na_2SO_4). The removal of solvent gave the final products (Table 2).

Pyrrolidinecarbothioic acid S-[(2,3-epithio)propyl] ester (**1**).

This compound was obtained as a colorless oil. ir (neat): 2967, 2874, 1651 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.89-1.96 (m, 4H, CH_2 × 2 pyrrolidine), 2.31-2.35 (dd, J=5.2, 1.1 Hz, 1H, 1-CH_2), 2.52-2.55 (d, J=6.0 Hz, 1H, 1-CH_2), 2.98-3.05 (dd, J=10.4, 5.8 Hz, 1H, 3-CH_2), 3.06-3.31 (m, 1H, 2-CH), 3.32-3.41 (m, 3H, 3-CH_2 & N-CH_2 pyrrolidine), 3.50-3.56 (m, 2H, N-CH_2 pyrrolidine); ^{13}C nmr (deuteriochloroform): δ 24.96, 25.95, 26.52, 34.73, 46.15, 46.38, 47.64, 165.24; ms (FAB): m/z 204 (M^++1), 170, 105.

Anal. Calcd. for $C_8H_{13}NOS_2$: C, 47.29; H, 6.40; N, 6.89. Found: C, 47.40; H, 6.21; N, 6.53.

Morpholinecarbothioic Acid S-[(2,3-epithio)propyl] Ester (**2**).

This compound was obtained as a white solid; mp 65-67 °C; ir (potassium bromide): 2910, 2862, 1648 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30-2.33 (dd, J=5.1, 1.2 Hz, 1H, 1-CH_2), 2.53-2.56 (d, J=5.2 Hz, 1H, 1-CH_2), 3.01-3.16 (m, 2H, 2-CH & 3-CH_2), 3.32-3.39 (dd, J=10.7, 4.7 Hz, 1H, 3-CH_2), 3.56-3.71 (m, 8H, 4 × CH_2 morpholine); ^{13}C nmr (deuteriochloroform): δ 26.52, 34.46, 36.86, 45.49, 66.88,167.10; ms (FAB): m/z 220 (M^++1), 114.

Anal. Calcd. for $C_8H_{13}NO_2S_2$: C, 43.83; H, 5.93; N, 6.39. Found: C, 43.71; H, 6.07; N, 6.51.

N-Methyl-*N*-benzylaminocarbothioic Acid S-[(2,3-epithio)propyl] Ester (**3**).

This compound was obtained as light yellow oil; ir (neat): 2925, 1652, 1080 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.31-2.34 (dd, J=5.2, 1.2 Hz, 1H, 1-CH_2), 2.54-2.57 (d, J=6.1 Hz, 1H, 1-CH_2), 2.89-2.98 (dd, J=11.6, 5.8 Hz, 1H, 3-CH_2), 3.10 (m, 1H, 2-CH), 3.15-3.20 (dd, J=11.7, 5.8, 1H, 3-CH_2), 3.23(s, 3H, N-CH_3), 3.33-3.40(m, 2H, benzyl CH_2), 6.76-6.88 (m, 3H, phenyl), 7.14-7.23(m, 2H, phenyl); ^{13}C nmr (deuteriochloroform): δ 26.4, 34.8, 37.2, 45.4, 67.2, 128.1, 129.1, 166.3; ms (FAB): m/z 254 (M^++1), 227, 191.

Anal. Calcd. for $C_{12}H_{15}NOS_2$: C, 56.91; H, 5.92; N, 5.53. Found: C, 56.73; H, 5.78; N, 5.64.

Hexamethyleneiminecarbothioic Acid S-[(2,3-epithio)propyl] Ester (**4**).

This compound was obtained as a light yellow oil; ir (neat): 2929, 2859, 1646 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.57-1.60 (m, 4H, CH_2 × 2), 1.74 (m, 4H, CH_2 × 2), 2.30-2.34 (dd, J=5.2, 1.2 Hz, 1H, 1-CH_2), 2.52-2.55 (d, J=6.0 Hz, 1H, 1-CH_2), 2.98-3.04 (dd, J=10.3, 5.8 Hz, 1H, 3-CH_2), 3.31 (m, 1H, 2-CH), 3.40-3.49 (dd, J=11.3, 5.8, 5Hz, 1H, 3-CH_2), 3.54-3.60 (m, 4H, N-CH_2 × 2); ^{13}C nmr (deuteriochloroform): δ 26.5, 27.3, 28.2.34.7, 36.9, 48.1, 166.3; ms (FAB): m/z 232 (M^++1), 137, 126.

Anal. Calcd. for $C_{10}H_{17}NOS_2$: C, 51.94; H, 7.35; N, 6.06. Found: C, 51.82; H, 7.56; N, 6.14.

4-(3-Chloro)phenyl-1-piperazinecarbothioic Acid S-[(2,3-epithio)propyl] Ester (**5**).

This compound was obtained as a yellow oil; ir (neat): 2921, 2850, 1649, 1593 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.31-2.34 (d, J=5.2 Hz, 1H, 1-CH_2), 2.54-2.59 (m, 1H, 1-CH_2), 3.09-3.22 (m, 4H, CH_2 × 2-piperazine), 3.34-3.49 (m, 3H, 2-CH & 3-CH_2), 3.59-3.71 (m, 4H, CH_2 × 2-piperazine), 6.75-6.88 (m, 3H, Ar CH), 7.15-7.26 (m, 1H, Ar CH); ^{13}C nmr (deuteriochloroform): δ 26.5, 34.4, 36.9, 48.4, 49.2, 76.7, 77.4, 78.6, 114.9, 116.9, 120.7, 130.6, 135.5, 152.5, 167.2; ms (FAB): m/z 329 (M^++1), 328 (M^+), 255, 223.

Anal. Calcd. for $C_{14}H_{17}ClN_2OS_2$: C, 51.14; H, 5.17; N, 8.52. Found: C, 51.01; H, 5.24; N, 8.38.

4-(2-Pyridyl)-1-piperazinecarbothioic Acid S-[(2,3-epithio)propyl] Ester (**6**).

Compound is white solid; mp 84-86 °C; ir (potassium bromide): 2989, 2834, 1640, 1594 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.32-2.34 (d, J=4 Hz, 1H, 1-CH_2), 2.55-2.57 (d, J=4 Hz, 1H, 1-CH_2), 3.01-3.08 (dd, J=9, 6, 4 Hz, 1H, 3-CH_2), 3.15-3.23 (m, 1H, 2-CH), 3.36-3.43 (dd, J=10, 4Hz, 1H, 3-CH_2), 3.61-3.74 (m, 8H, CH_2 × 4-piperazine), 6.64-6.70 (m, 2H, Ar CH), 7.49-7.54 (m, 1H, Ar CH), 8.20-8.21 (m, 1H, Ar CH); ^{13}C nmr (deuteriochloroform): δ 26.5, 34.4, 36.9, 48.3, 49.2, 107.6, 114.4,138.0, 148.4, 159.2, 166.9; ms (FAB): m/z 296 (M^++1), 264, 222, 190.

Anal. Calcd. for $C_{13}H_{17}N_3OS_2$: C, 52.88; H, 5.76; N, 14.23. Found: C, 52.80; H, 5.83; N, 14.07.

4-(2-Pyrimidyl)-1-piperazinecarbothioic Acid S-[(2,3-epithio)propyl] Ester (**7**).

This compound was obtained as a white solid; mp 97-99 °C; ir (potassium bromide): 2919, 2853, 1642, 1586 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.32-2.35 (dd, J=5.2, 1.1 Hz, 1H, 1-CH_2), 2.54-2.57 (d, J=6 Hz, 1H, 1-CH_2), 2.99-3.09 (dd, J=13.1, 7.4 Hz, 1H, 3-CH_2), 3.16-3.19 (m, 1H, 2-CH), 3.35-3.44 (dd, J=13, 4.4 Hz, 1H, 3-CH_2), 3.64-3.85 (m, 4H, CH_2 × 2-piperazine), 3.87-3.90 (m, 4H, CH_2 × 2-piperazine), 6.52-6.57 (t, J=4.7Hz, 1H, Ar CH), 8.31-8.34 (t, J=4.7 Hz, 2H, Ar CH); ^{13}C nmr (deuteriochloroform): δ 26.5, 34.4, 36.9, 43.8, 110.9, 158.1, 161.9, 170.2; ms (FAB): m/z 297(M^++1), 296(M^+), 265, 225, 191.

Anal. Calcd. for $C_{12}H_{16}N_4OS_2$: C, 48.64; H, 5.40; N, 18.91. Found: C, 48.70; H, 5.61; N, 18.80.

3-Methylpiperidinecarbothioic Acid S-[(2,3-epithio)propyl] Ester (**8**).

This compound was obtained as a colorless oil; ir (neat): 2929, 2856, 1650, 1411, 1215 cm^{-1}; ^1H nmr (deuteriochloroform): δ

0.90-0.93 (d, J=6.6Hz, 3H, 3-CH_3 piperidine), 1.22-1.30 (m, 1H, 3-CH piperidine), 1.52-1.68 (m, 4H, CH_2 × 2-piperidine), 2.30-2.33 (d, J=5.2 Hz, 1H, 1- CH_2), 2.52-2.55 (d, J=5.8 Hz, 1H, 1- CH_2), 2.93-3.04 (dd, J=13.3, 7.4 Hz, 1H, 3- CH_2), 3.14-3.17 (m, 1H, 2-CH), 3.31-3.40 (dd, J=15.4, 4.2 Hz, 1H, 3- CH_2), 3.68-3.96 (m, 4H, N- CH_2 × 2-piperidine); ^{13}C nmr (deuteriochloroform): δ 19.1, 25.4, 26.5, 31.5, 33.3, 34.6, 36.9, 46.1, 149.7, 166.1; ms (FAB): m/z 232 (M^++1), 172, 126, 105.

Anal. Calcd. for $C_{10}H_{17}NOS_2$: C, 51.94; H, 7.35; N, 6.06. Found: C, 52.04; H, 7.27; N, 6.17.

Piperidinecarbothioic Acid S-[(2,3-epithio)propyl] Ester (**9**).

This compound was obtained as a light yellow oil; ir (neat): 2937, 2857, 1649 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.52 (m, 6H, CH_2 × 3-piperidine), 2.30-2.33 (d, J=5.32, 1.2 Hz, 1H, 1- CH_2), 2.53-2.56 (d, J=6.1 Hz, 1H, 1- CH_2), 2.93-3.03 (dd, J=13.3, 7.4 Hz, 1H, 3- CH_2), 3.14-3.21 (m, 1H, 2-CH), 3.31-3.40 (dd, J=13.3, 4.8 Hz, 1H, 3- CH_2), 3.49-3.68 (m, 4H, CH_2 × 2-piperidine); ms (FAB): m/z 218 (M^++1), 217 (M^+), 186, 112.

Anal. Calcd. for $C_9H_{15}NOS_2$: C, 49.76; H, 6.91; N, 6.45. Found: C, 49.51; H, 6.82; N, 6.34.

Pyrrolidinecarbodithioic Acid S-[(3-chloro-2-hydroxy)propyl] Ester (**Intermediate III**) [5].

This compound was obtained as a colorless semi solid; uv (methanol, λ_{max}, nm.): 272.8, 245.2, 218.0. ^{1}H nmr (deuteriochloroform): δ 1.96-2.13 (m, 4H, CH_2 × 2-pyrrolidine), 3.57-3.73 (m, 6H, CH_2 × 2-pyrrolidine & 3- CH_2), 3.90-3.97 (m, 2H, 1- CH_2), 4.10-4.19 (m, 1H, 2-CH); ms (FAB): m/z 240 (M^++1), 204.

Acetylation.

A solution of pyrrolidinecarbodithioic acid sodium salt (3 mmol) in water (10 ml) was cooled in an ice bath (0-5 °C) for 15-30 minutes. Epichlorohydrin (1.5 equivalent) was added dropwise with stirring. The reaction mixture became turbid within 2–5 minutes and continued stirring in an ice bath for 30 minutes. Then benzene (5 ml) was added and the contents were transferred into a test tube and centrifuged at –10 °C to separate the two layers. Then the organic layer was separated using snap freeze technique and kept stirring in ice bath (0-5 °C) for 15 minutes. Then acetyl chloride (2 equivalent) was added in parts and stirring was continued till the reaction is completed (as monitored by TLC). Then the reaction mixture was diluted with 10 ml EtOAc and the combined organic layer was washed with water (5ml × 4) and dried (anhydrous Na_2SO_4). The removal of solvent gave the acetylated product.

Pyrrolidinecarbodithioic Acid S-[(2-acetoxy-3-chloro)propyl] Ester.

This compound was obtained as a light yellow oil; ir (neat): 3021, 2972, 1746, 1657-1584, 1370, 1040 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.99-2.22 (m, 7H, CH_2 × 2-pyrrolidine, $COCH_3$), 3.63-3.95 (m, 8H, 3- CH_2, 1- CH_2, CH_2 × 2- pyrrolidine), 5.15-5.20 (m, 1H, 2-CH); MS (FAB): m/z 284 (M+3), 282(M+1), 246, 207.

Anal. Calcd. for $C_{10}H_{16}ClNO_2S_2$: C, 42.62; H, 5.68; N, 4.97. Found: C, 42.31; H, 5.49; N, 4.79.

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REFERENCES AND NOTES

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[1] W. C. Doyle Jr., US patent 3,510,290 (1970); *Chem. Abstr.*, **73**, 35210 (1970).

[2] W. C. Doyle Jr., US patent 3,561,949 (1971); *Chem. Abstr.*, **74**, 87809 (1971).

[3] W. C. Doyle Jr., US patent 3,634,457 (1972); *Chem. Abstr.*, **77**, 34286 (1972).

[4] W.C. Doyle Jr., US patent 3,676,479 (1972); *Chem. Abstr*., **77**, 100872 (1972).

[5] W. C. Doyle Jr., US patent 3,728,371 (1973); *Chem. Abstr*., **79**, 5246 (1973).

[6] W.C. Doyle Jr., US patent 3,723,493 (1973); *Chem. Abstr*., **78**, 158995 (1973).

[7] H. Camenzind, P.Dubs, Eur. Pat. Appl. EP 211, 806 (1987); *Chem. Abstr*. **107**, 42895 (1987).

[8] N. A. Nedolya, V. I. Dymchenko, R. L.Yanilkina, *Zh. Org. Khim.,* **26**, 993-8 (1990); *Chem. Abstr*., **113**, 171803 (1990).

[9] S. Fujisaki, T. Nishi, A. Nishida, S. Kajigaeshi, *Technol. Rep. Yamaguchi Univ.*, **4**, 71 (1987); *Chem. Abstr*., **109**, 230906 (1987).

[10] R. Bryant, " Putting Partnership Back into Process Chemistry", Scrip Magazine, December, 13 (2002).

[11] H. C. Van Der Plas, Ring Transformations of Heterocycles, Vol I, Academic press, New York & London, 1973, 3, 20.

[12] Rollin, P., *Tetrahedron Lett.*, **27**, 4169 (1986).