ONE STEP SYNTHESIS OF 5-BROMO-2-CHLORO-6-HYDROXY-4-[N-(2,3-DIBROMOPROPYL)-N-ALKYLAMINO]PYRIMIDINES, USEFUL INTERMEDIATES FOR THE PREPARATION OF PTERIDINE DERIVATIVES AND RELATED ANALOGUES

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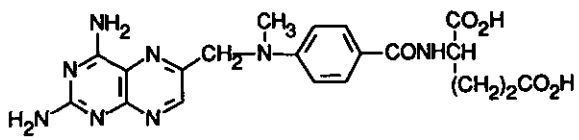
Abstract - A simple synthesis of pteridine derivatives (12) and (13), 5-oxapteridines (10 a-c) and 5-thiapteridine (15) via cyclization of the highly functionalized pyrimidinones (8 a-c) is reported.

Pteridines are very common products in both the animal and plant kingdoms. Many of them are biologically active and structural analogues possess drug type properties,[1] such as growth-inhibition,[2] antitumor[3] and antimalarial[4] activities. Generally pteridines possess a broad spectrum of activity as dihydrofolate reductase (DHFR) inhibitors,[5] metotrexate (1) (MTX) being the most important example.[6]



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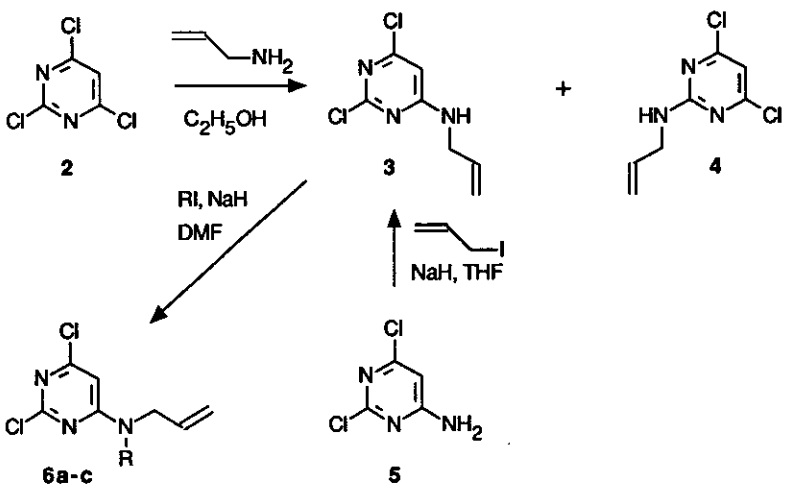
The development of analogues with potentially superior clinical properties or a sole DHFR inhibiting action is generally held to have little promise. However the design of folate analogues, which act as substrates for DHFR to produce "spurious" coenzymes inhibiting other enzymes in the folate cycle, remains an attractive rational strategy.

The isosteric substitution of the N-5 nitrogen of pteridine nucleus seems to be very little studied even if some pyrimido[4,5-b][1,4]oxazines (5-oxadihydropteridines) have recently shown interesting bronchodilator,[7] cardiotonic,[8] and antitumor[9] activities.

Following our study on C-6 substituted 4(3H)-pyrimidinones as precursors for the synthesis of new antiviral and antitumor agents,[10] we are reporting in the present paper the one-step preparation of the tribromo derivatives (8 a-c) and their use in the synthesis of the 5-oxapteridine analogues (10 a-c) as well as the synthesis of the pteridine derivatives (12) and (13) and the 5-thiaanalogue (15).

Commercially avalaible 2,4,6-trichloropyrimidine (2) was reacted with allylamine in dry ethanol at room temperature to give predominantly 4-allylamino-2,6-dichloropyrimidine (3) (75%) along with the undesired C-2 isomer 4 (23%) (Scheme 1). The structure of compound (3) was confirmed by the allylation of 4-amino-2,6-dichloropyrimidine (5). Subsequent alkylation of the exocyclic nitrogen of 3 with the suitable alkyl iodide in DMF in the presence of NaH afforded the 4-N,N-dialkylaminopyrimidines (6 a-c) in good yields.

Scheme 1

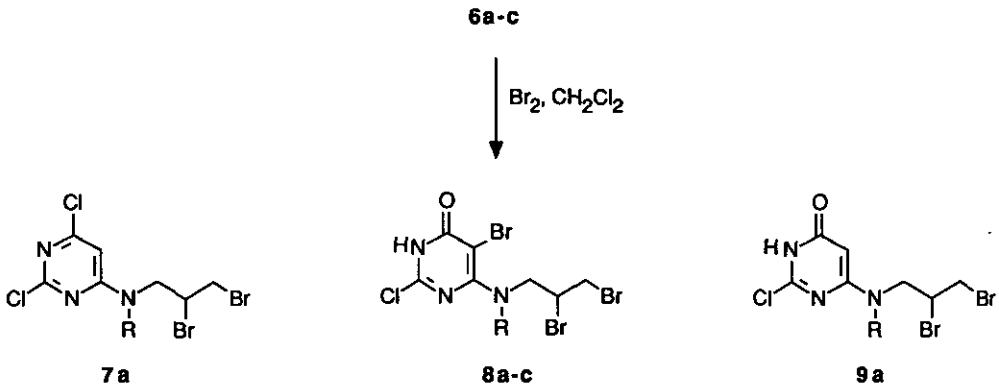


a: R = CH_3; **b**: R = C_2H_5; **c**: R = $CH_2C_6H_5$

The bromination of the side chain double bond in 6a with an excess of bromine in CH_2Cl_2 at room temperature gave the expected product (7a) along with the tribromo derivative (8a) and a small amount of 9a (Scheme 2). The bromination reaction in freshly distilled CH_2Cl_2 afforded two products (7a) and (9a). When performed in

freshly distilled CH_2Cl_2, with 1.1 mole of bromine in the presence of Na_2CO_3 under nitrogen, the reaction afforded 7a as a single product.
In the above reactions, the hydrolysis of 7a to 9a would be due to moisture in the solvent, and the subsequent reaction of 9a with an excess of bromine provided the tribromide (8a).

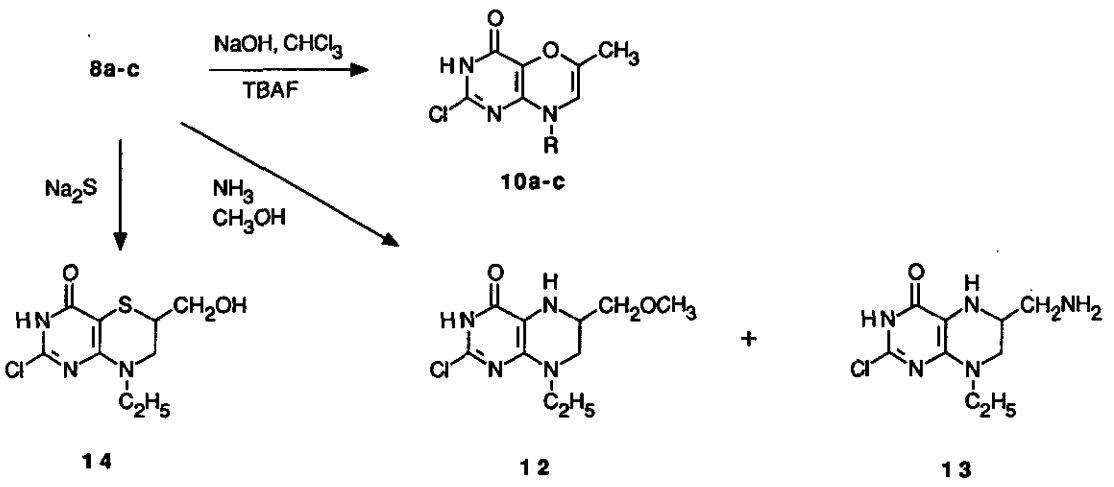
Scheme 2



a: R = CH_3; **b**: R = C_2H_5; **c**: R = $CH_2C_6H_5$

The reaction using a large excess of bromine in wet CH_2Cl_2 for longer reaction time gave directly 8a in good yield.
The structure of the bromination products, easily distinguishable by tlc, has been assigned on the basis of the ^{1}H-nmr (lack of the C-5 proton absorbtion in the spectrum of compound (8a)) and ir (presence of a carbonyl at ν 1680 cm^{-1} in the spectra of compounds (9a) and (8a)).
The tribromo derivative (8a) was found to be a versatile synthon for the synthesis of bicyclic compounds structurally related to pteridines. In fact, when 8a was allowed to react in $CHCl_3$/ NaOH (10% aqueous solution) in the presence of tetra-n-butylammonium fluoride (TBAF) as a phase transfer catalyst, 10a was obtained in 55% yield (Scheme 3).
The tribromo derivatives (8b,c) prepared in a similar manner to the above were also transformed into compounds (10b,c) in 47% and 58% yields, respectively.
It seems likely that this cyclization proceeds via an initial substitution of the side chain secondary bromine atom with hydroxy anion and anchimerically assisted by the α-nitrogen,[11] followed by the intramolecular displacement of the nuclear C-5 bromine. Subsequent HBr elimination affords the exocyclic double bond, which then shifts in the more stable endocyclic position.

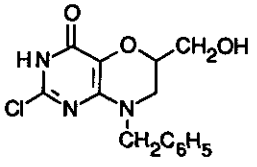
Scheme 3



a : R = CH_3; **b** : R = C_2H_5; **c** : R = $CH_2C_6H_5$

In the case of the cyclization of 8c, compound (11) was also obtained as a by-product. This product, upon treatment with sulfuric acid, gave the expected 10c.

The tribromo derivatives (8) were shown to be good synthons to obtain pteridines and 5-thiapteridines. When 8b was allowed to react with ammonia in dry methanol at -20 °C for 6 h the pteridines (12) (52%) and (13) (26%) were obtained. On the other hand, the reaction of 8b with Na_2S in aqueous methanol solution at room temperature for 6 h afforded the 5-thia derivative (14) (33%). At variance with the cyclization leading to the 5-oxa analogues, the primary bromine of side chain in the last two cases underwent displacement with nucleophiles instead of elimination.



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More work in the direction of these transformations is already in course in our laboratories as well as biological evaluation of the synthesized bicyclic derivatives.

EXPERIMENTAL

Nmr spectra were recorded on a Varian XL 300 (300 MHz) spectrometer and are reported in δ values. Melting points were obtained on a Reichert Kofler apparatus and are uncorrected. Microanalyses were performed by C. Erba 1106 analyzer. Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer using NaCl plates. Mass spectra were recorded on a Kratos MS80 spectrometer. All solvents were ACS reagent grade and were redistilled and dried according to standard procedure. Chromatographic purification were performed on columns packed with Merck silica gel 60, 230-400 mesh for flash technique. Preparative tlc was performed with C. Erba silica gel Stratocrom SIF-254 precoated plates.

Procedure for the synthesis of 3

To a solution of 2,4,6-trichloropyrimidine (2) (3.66 g, 20 mmol) in dry EtOH (30 ml) was added allylamine (1.42 g, 25 mmol) dropwise at room temperature. After 1 h the mixture was evaporated and the resultant oil was dissolved in CH_2Cl_2 (20 ml). The organic layer was washed with Na_2CO_3 (10% solution), NaCl (saturated solution), dried (Na_2SO_4) and evaporated under reduced pressure. The resultant foam was purified by flash chromatography on silica gel ($CHCl_3$/MeOH; 9/1) to give 3 and 4 in 75% and 25% yields, respectively.

3: mp 68-70°C (n-hexane); ir (ν, cm^{-1}) ($CHCl_3$) 3480,1590; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 3.93 (s, 2H, CH_2), 5.22 (m, 2H, CH_2), 5.82 (m, 1H, CH), 6.26 (s, 1H, CH); ms $^+$EI (m/z , M^++1) 204. Anal. Calcd for $C_7H_7N_3Cl_2$: C,41.20; H,3.46; N,20.59. Found: C,41.15; H, 3.48; N,20.60.

4: mp 71-73°C (n-hexane); ir (ν, cm^{-1}) ($CHCl_3$) 3480,1590; ^{1}Hnmr (δ, ppm) ($CDCl_3$): 4.07 (m, 2H, CH_2), 5.19 (m, 2H, CH_2), 5.90 (m, 1H, CH), 6.59 (s, 1H, CH); ms $^+$EI (m/z, M^++1) 205. Anal. Calcd for $C_7H_7N_3Cl_2$: C,41.20; H,3.46; N, 20.59. Found: C, 41.18; H, 3.44; N, 20.61.

General procedure for the synthesis of 6a,b,and c.

To a solution of 3 (1.63 g, 8 mmol) in dry DMF (10 ml) was added NaH (0.20 g, 8.5 mmol) slowly and the mixture was stirred for 10 min at room temperature. Then, alkyl iodide (8.5 mmol) was added dropwise. After 3 h water (20 ml) was added to

the mixture. The organic layer diluted with EtOAc was separated, washed many times with water (20 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The resultant yellow oil was purified by flash chromatography on silica gel (n-hexane/$CHCl_3$=8/2) to give the products:
6a: Yield 90%, oil; ir (ν, cm^{-1}) ($CHCl_3$),1580; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 3.00 (s, 3H, CH_3), 4.10 (m, 2H, CH_2), 5.15 (m, 2H, CH_2), 5.70 (m, 1H, CH), 6.25 (s, 1H, CH); ^{13}Cnmr (δ, ppm) ($CDCl_3$) 35.27 (CH_3), 51.62 (CH_2), 99.58 (CH), 117.70 (CH_2), 131.43 (CH), 159.52 (C), 159.9 (C), 163.4 (C) ; ms $^+$EI (m/z, M^++1) 219. Anal. Calcd for $C_8H_9N_3Cl_2$: C, 44.06; H, 4.16; N, 19.26. Found: C, 44.10; H, 4.15; N, 19.26.

6b: Yield 93%, oil; ir (ν, cm^{-1}) ($CHCl_3$), 1580; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 1.05 (t, J = 7Hz, 3H, CH_3), 3.80 (m, 2H, CH_2), 5.10 (m, 2H, CH_2), 5.70 (m, 1H, CH), 6.20 (s, 1H, CH); ^{13}Cnmr (δ, ppm) ($CDCl_3$) 27.30 (CH_3), 33.20 (CH_2), 33.22 (CH_2), 100.01 (CH), 120.10 (CH_2), 135.0 (CH), 148.52 (C), 159.8 (C), 164.10 (C); ms $^+$EI (m/z, M^++1) 233. Anal. Calcd for $C_9H_{11}N_3Cl_2$: C,46.58; H,4.78; N,18.10. Found : C, 46.55; H, 4.78; N, 18.06.

6c: Yield 95%, oil; ir (ν, cm^{-1}) ($CHCl_3$),1560; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 4.10 (m, 4H, CH_2), 5.20 (m, 2H, CH_2), 5.75 (m, 1H, CH), 6.30 (s, 1H, CH), 7.10-7.45 (m, 5H); ^{13}Cnmr (δ, ppm) ($CDCl_3$) 50.06 (CH_2), 50.80 (CH_2), 100.10 (CH), 118.15 (CH_2), 127.90 (CH), 127,97 (CH), 128.22 CH), 129.07 (CH), 138.40 (C), 159.72 (C), 160.30 (C), 163.67 (C); ms $^+$EI (m/z, M^++1) 295. Anal. Calcd for $C_{14}H_{13}N_3Cl_2$: C,57.15; H,4.45; N, 14.28. Found: C, 57.18; H, 4.50; N, 14.30.

General procedure for the synthesis of 8a,b and c

To a solution of 6a,b,c (2 mmol) in wet CH_2Cl_2 (10 ml; 5 mmol of H_2O were added) was added bromine (6 ml, 11 mmol, 10% CH_2Cl_2 solution) at room temperature. After 4 h the mixture was decomposed by the addition of $Na_2S_2O_3$ (3 ml, 10% aqueous solution). The organic layer was separated , washed with $NaHCO_3$ (saturated water solution), dried (Na_2SO_4) and evaporated under reduced pressure. The resultant oil was purified by column chromatography on silica gel using $CHCl_3$/MeOH (9.5/0.5) as the solvent to give the products (8a,b,c) in the yields reported below:
8a: Yield 52%; mp 150-152 °C (MeOH/H_2O); ir (ν, cm^{-1}) ($CHCl_3$) 1670,1590; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 3.43 (s, 3H, CH_3), 3.50-3.70 (m, 2H, CH_2), 3.91-4.25 (m, 2H, CH_2), 4.80 (m, 1H, CH); ms $^+$EI(m/z, M^++1) 439. Anal. Calcd for $C_8H_9N_3OBr_3Cl$: C, 21.92; H, 2.07; N, 9.59. Found: C, 21.95; H, 2.10; N, 9.58.

8b: Yield 57%; mp 153-155 °C (MeOH/H_2O); ir (ν, cm^{-1}) ($CHCl_3$) 1670,1590; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 1.15 (t, J = 7 Hz, 3H, CH_3), 3,45-4.20 (m, 6H, CH_2), 4.80 (m, 1H, CH); ms $^+$EI (m/z, M^++1) 453. Anal. Calcd for $C_9H_{11}N_3OBr_3Cl$: C, 23.90; H, 2.45; N, 9.29. Found: C, 23.85; H, 2.50; N, 9.23.

8c: Yield 92%; mp 140-142 °C (MeOH/H_2O); ir (ν, cm^{-1}) ($CHCl_3$) 1680,1580; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 3.60 (m, 2H, CH_2), 4.10 (m, 2H, CH_2), 4.81 (m, 1H, CH), 5.10 (m, 2H, CH_2), 7.20-7.41 (m, 5H, CH); ms $^+$EI (m/z, M^++1) 515. Anal. Calcd for $C_{14}H_{13}N_3OBr_3Cl$: C, 32.69; H, 2.55; N, 8.17. Found: C, 32.70; H,2.56; N, 8.15.

When the reaction was run with bromine (0.08 ml, 1.6 mmol) in CH_2Cl_2 7a and 9a were also obtained:
7a: Yield 13%; oil; ir (ν, cm^{-1}) ($CHCl_3$) 1580; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 3.20, (s, 3H, CH_3), 3.61-3.85 (m, 3H), 4.30-4.70 (m, 2H, CH_2); 6.42 (s, 1H, CH); ms $^+$EI (m/z, M^++1) 379. Anal. Calcd for $C_8H_9N_3Br_2Cl_2$: C, 25.43; H, 2.39; N, 11.12. Found: C, 25.45; H, 2.37; N, 11.09.

9a: Yield 6%; oil; ir (ν, cm^{-1}) ($CHCl_3$) 1620, 1680; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 3.45 (s, 3H, CH_3), 3.60-3.85 (m, 2H, CH_2), 3.85-3.95 (m, 1H, CH), 4.10-4.15 (m, 2H, CH_2), 3.90 (m, 1H, CH), 4.0-5.10 (m, 2H, CH_2), 5.55 (s, 1H, CH); ms $^+$EI (m/z, M^+) 359. Anal. Calcd for $C_8H_{10}N_3OBr_2Cl$: C, 26.73 ; H, 2.80 ; N, 11.69 . Found: C, 26.80 ; H, 2.85 ; N, 11.65 .

General procedure for the synthesis of 10a,b,c and 11.

To a solution of 8a,b,c (2 mmol) in $CHCl_3$ (8 ml) NaOH (5 ml, 16 mmol; 10% aqueous solution) was added in the presence of TBAF (catalytic amount). After 16 h the mixture was neutraziled and the solvent was evaporated under reduced pressure. The resultant foam was purified by column chromatography on silica gel using $CHCl_3$/MeOH (8/2) as the solvent to afford the products.
10a: Yield 55%; mp 153-155°C (MeOH/H_2O); ir (ν, cm^{-1}) ($CHCl_3$) 3600,1680; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 2.60 (s, 3H, CH_3), 4.05 (s, 3H, CH_3), 6.80 (s, 1H, CH); ms $^+$EI (m/z, M^+) 214. Anal. Calcd for $C_8H_8N_3O_2Cl$: C, 44.98; H, 3.77; N, 19.67. Found: C, 45.00; H, 3.77; N,19.68.

10b: Yield 47%; mp 170-172°C (MeOH/H_2O); ir (ν, cm^{-1}) ($CHCl_3$) 3600,1680,1560; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 1.49 (t, J = 7 Hz, 3H, CH_3), 2.65 (s, 3H, CH_3), 4.48 (m, 2H, CH_2), 6.63 (s, 1H, CH); ms $^+$EI (m/z, M^+) 228. Anal. Calcd for $C_9H_{10}N_3O_2Cl$: C, 47.48; H, 4.43; N, 18.46. Found: C, 47.51, H,4.50, N, 18.48.

10c: Yield 57.5%; mp 218-220°C (MeOH/H_2O); ir (ν, cm^{-1}) ($CHCl_3$) 3600,1680,1590; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 2.70 (s, 3H, CH_3), 5.65 (m, 2H, CH_2), 6.60 (s, 1H, CH), 7.11-7.40 (m, 5H, CH); ms $^+$EI (m/z, M^+) 290. Anal. Calcd for $C_{14}H_{12}N_3O_2Cl$: C, 58.04; H, 4.17; N, 14.50. Found; C, 58.10; H, 4.20; N, 14.52.

In the case of the reaction of 8c compound 11 was also obtained :
11: Yield 23.8%; oil; ir (ν, cm^{-1}) ($CHCl_3$) 3600,3400,1690,1590; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 3.90-4.90 (m, 2H, CH_2), 4.35 (m, 2H, CH_2), 5.10 (m, 2H, CH_2), 6.51 (m, 1H,

CH), 7.22-7.41 (m, 5H); ms +EI (m/z, M^+) 308. Anal. Calcd for $C_{14}H_{14}N_3O_3Cl$: C, 54.64; H, 4.58; N, 13.65. Found: C, 54.66; H, 4.56; N, 13.65.

Procedure for the synthesis of 12 and 13.

To a solution of 8b (0.9 g, 2 mmol) in MeOH (5 ml) was added ammonia (MeOH saturated solution) at -5 °C under N_2. After 7 h the solvent was evaporated under reduced pressure and the resultant foam was purified by preparative tlc ($CHCl_3$/MeOH; 9.5/0.5) to give products 12 and 13.
12: Yield 52%; mp 278-280°C (MeOH/H_2O); ir (ν, cm^{-1}) ($CHCl_3$) 3600,1680; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 1.19 (t, J = 7 Hz, 3H, CH_3), 3.14 (s, 3H, CH_3), 3.55 (q, J = 7 Hz, 2H, CH_2), 4.25 (m, 2H, CH_2), 4.55 (m, 1H, CH), 4.60 (m, 1H, CH), 6.11 (m, 1H, CH) ; ms +EI (m/z, M^+) 259. Anal. Calcd for $C_{10}H_{15}N_4O_2Cl$: C, 46.42; H, 5.84; N, 21.66. Found: C, 46.68, H, 5.81; N, 21.70.

13: Yield 26%; oil; ir (ν, cm^{-1}) ($CHCl_3$) 3400,1680,1600; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 1.26 (t, J = 7 Hz, 3H, CH_3), 3.84 (q, J = 7 Hz, 2H, CH_2), 3.97 (m, 2H, CH_2), 4.36 (m, 2H, CH_2), 6.34 (m, 1H, CH); ms +EI (m/z, M^++1) 245. Anal. Calcd for $C_9H_{14}N_5OCl$: C, 56.23; H, 7.34; N, 36.43. Found: C, 56.83; H,5.76; N, 28.80.

Procedure for the synthesis of 14.

To a solution of 8b (0.9 g, 2 mmol) in MeOH (5 ml) was added Na_2S (0.16 g, 2 mmol) at room temperature. After 3 h the solvent was evaporated under reduced pressure and the resultant oil was purified by preparative tlc ($CHCl_3$/MeOH=9.5/0.5) to give product (14).
Yield 33%; oil; ir (ν, cm^{-1}) ($CHCl_3$) 3600,3400,1680,1600; ^{1}Hnmr (δ, ppm) ($CDCl_3$) 1.23 (m, 3H, CH_3), 3.80 (m, 2H, CH_2), 3.91 (m, 2H, CH_2), 4.38 (m, 1H), 4.78 (m, 1H), 6.25 (m, 1H, CH); ms +EI (m/z, M^+) 262. Anal. Calcd for $C_9H_{12}N_3O_2ClS$: C, 41.31; H, 4.62; N, 16.05. Found: C, 41.33; H, 4.62; N, 16.00.

ACKNOWLEDGMENT

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