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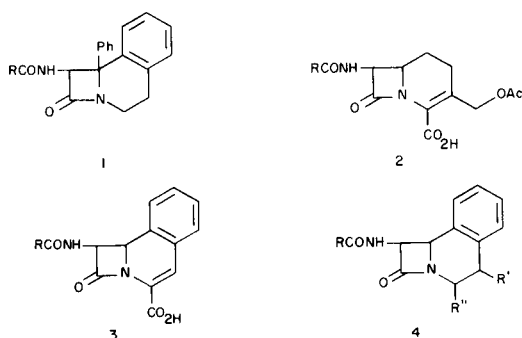
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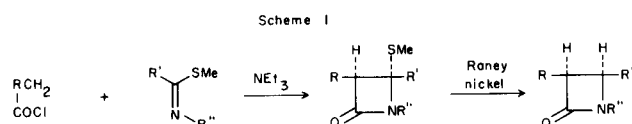
The strategy used for the stereospecific synthesis of benzofused octams as cepham analogs was the conversion of a 3,4-dihydrothioisocarbostyryl to a thioimide, cycloaddition reaction to form a fused  $\beta$ -lactam and subsequent removal of the alkylthio group by Raney nickel hydrogenolysis. Using azidoacetyl chloride for forming the  $\beta$ -lactam and following known procedures, an amido side chain was generated. Two of the carba analogs of cephalosporin so produced showed low levels of antibacterial activity against a number of gram positive and gram negative organisms.

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The first synthesis of carba analogs (1) of cephalosporin was reported by Bose and co-workers (2) in 1967. Since then a number of publications have appeared from this laboratory which describe the synthesis of carba analogs of penicillin (3) and cephalosporin (4). Christensen and co-workers (5) have reported the synthesis of a carba analog (2) of cephalosporin which retains some of the antibiotic activity of the natural product. In a recent publication Finkelstein and co-workers (6) have described the synthesis of a benzo-fused analog (3) of 2. This prompts us to report our synthesis of a closely related family of compounds of the general structure 4 by a different, stereospecific approach.



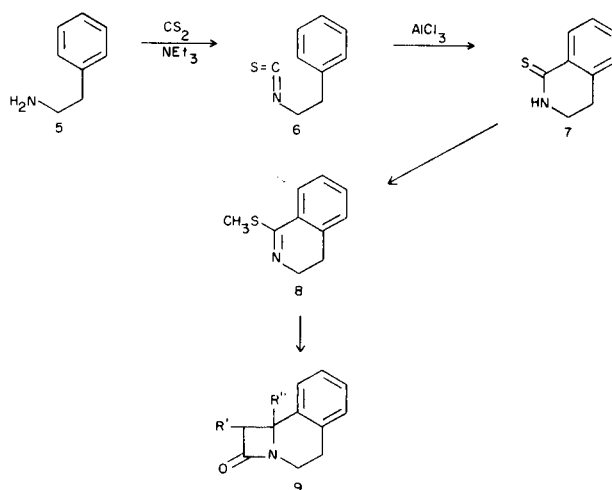
We have shown previously (7,8) that for reasons not clearly understood, the annelation of a thioimide with a substituted acetyl chloride and triethylamine leads stereospecifically to a monocyclic  $\beta$ -lactam in which the substituent group from the acid chloride and the mercapto group from the thioimide are *trans* to each other. Subsequent stereospecific hydrogenolysis (9) of the alkylthio group leads to a *cis*  $\beta$ -lactam (see Scheme 1). We have extended this synthetic approach for the preparation of 4.



Our first goal was the model compound (9). The cyclic thioamide (7) was prepared in good yield by a slight modification of a known method. Phenethylamine (5) was treated with carbon disulfide and alkali to form the isothiocyanate (6). Smith and Kan (10) have cyclized isothiocyanates to the corresponding thioamides in about 40% yield by reacting them with aluminum chloride in carbon bisulfide for 40 hours. We have found that the yield of the thioamide (7) could be doubled when the isothiocyanate (6) was refluxed for 3 hours with anhydrous aluminum chloride using methylene chloride as a solvent and a few drops of concentrated sulfuric acid as a catalyst. The methylation of 7 to 8 with methyl iodide proceeded smoothly in tetrahydrofuran (11).

The thioimide (8) showed stereospecificity in  $\beta$ -lactam formation. Reaction of 8 with methoxyacetyl chloride or

Scheme 2



R'	R''
a OCH <sub>3</sub>	SCH <sub>3</sub>
b N <sub>3</sub>	SCH <sub>3</sub>
c NH <sub>2</sub>	SCH <sub>3</sub>
d C <sub>6</sub> H <sub>5</sub> OCH <sub>2</sub> CONH	SCH <sub>3</sub>
e C <sub>6</sub> H <sub>5</sub> OCH <sub>2</sub> CONH	H (cis)

with azidoacetyl chloride in presence of triethylamine produced a single isomer of **9a** or **9b** in 50-60% yield. Catalytic hydrogenation of the azide to an amino compound and subsequent acylation led to the 7-amido-octam (**9d**) (12). Raney nickel hydrogenation of **9d** removed the methylthio group and a single isomer (**9e**) was obtained. The <sup>1</sup>H nmr spectrum of **9e** showed a coupling of 4 Hz between the β-lactam protons indicating *cis* stereochemistry for **9e**.

The same stereospecific synthesis was utilized for obtaining (**16d**). The preparation of the starting material, however presented some difficulties. Attempts to obtain **14** via the isothiocyanate route were unsuccessful. An alternative route shown in Scheme 3 was followed. Methyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**13**) was synthesized from phenylalanine using the method of Hein and Niemann (13) and transformed to the thioimidate (**15**) via the thioamide (**14**). The reaction of the appropriate substituted acetyl chlorides in the presence of triethylamine with **15** gave the octams (**16a-16d**).

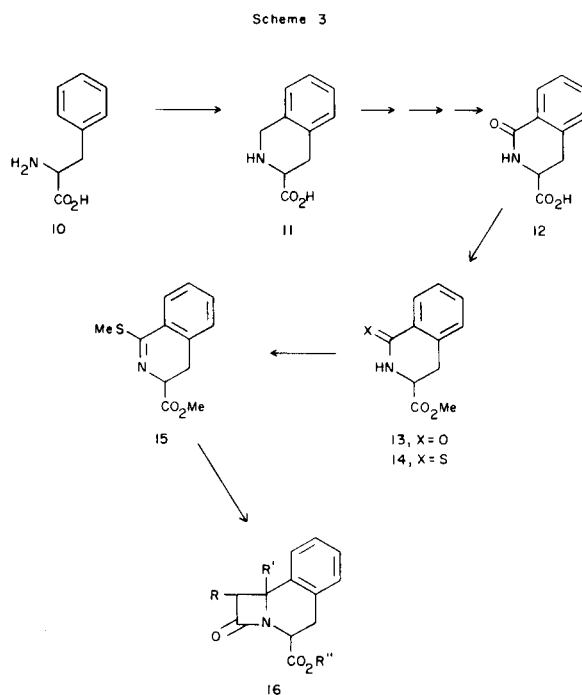
The hydrolysis of the model compound (**16a**) was attempted to generate the carboxy group α to the nitrogen atom of the β-lactam nucleus. It was observed that the best results were obtained by using 1% sodium hydroxide solution at 0°. Under these conditions the cleavage of the lactam ring was held to the minimum.

The 3-phenoxyacetyl-amido octam (**16g**) was obtained from **16d** by catalytic reduction followed by acylation of the intermediate amino derivative (**16f**).

Under the same conditions that were successful with **16a**, hydrolysis of **16g** resulted in the acid (**16h**) in poor yield. An analytically pure sample could not be prepared, but the ir, nmr and ms data were satisfactory.

Raney nickel treatment of the ester (**16g**) led to the *cis* octam (**16i**) which was hydrolyzed to the free acid (**16j**) in very low yield using the same technique as was successful for preparing **16a**. The ir and ms data for **16j** supported the structure assigned but the sample of **16j** was not analytically pure. Because of lack of material this sample of **16j** was submitted to biological screening without further purification.

The β-lactam (**16j**) showed MIC value (14) of 50 mcg./ml. against a number of gram positive and gram negative pathogens including *Brucella suis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *E. coli*. The mode of antibacterial action of **16j** is likely to be different from that for penicillins because the methyl ester (**16i**) also showed nearly the same level of antibiotic activity as the free acid. It is well-known that penicillin and cephalosporin esters are inactive as antibiotics unless they are first converted to the free acids in the animal system under test.



R	R'	R''
a C <sub>6</sub> H <sub>5</sub> O	SCH <sub>3</sub>	CH <sub>3</sub>
b CH <sub>3</sub> O	SCH <sub>3</sub>	CH <sub>3</sub>
c C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O	SCH <sub>3</sub>	CH <sub>3</sub>
d N <sub>3</sub>	SCH <sub>3</sub>	CH <sub>3</sub>
e C <sub>6</sub> H <sub>5</sub> O	SCH <sub>3</sub>	H
f NH <sub>2</sub>	SCH <sub>3</sub>	CH <sub>3</sub>
g PhOCH <sub>2</sub> CONH	SCH <sub>3</sub>	CH <sub>3</sub>
h PhOCH <sub>2</sub> CONH	SCH <sub>3</sub>	H
i PhOCH <sub>2</sub> CONH	H	CH <sub>3</sub> ( <i>cis</i> )
j PhOCH <sub>2</sub> CONH	H	H ( <i>cis</i> )

#### EXPERIMENTAL

Melting points were determined in open capillary tubes using a "Mel-Temp" apparatus and are uncorrected. Infrared spectra were obtained with a Perkin Elmer Infracord. Pmr spectra were recorded on a Varian A-60A spectrometer operating at 60 MHz in deuteriochloroform solution containing tetramethylsilane as an internal standard with chemical shifts ( $\delta$ ) expressed in ppm downfield from TMS. Mass spectra were obtained with a Perkin-Elmer RMU-7 mass spectrometer. Elemental analyses were performed by Bernhardt, Max-Planck Institute, Mülheim, West Germany. Florisil obtained from Fischer Scientific Company was used for chromatography. All solvents used were reagent grade. Distilled solvents were purified by distillation from phosphorus pentoxide. Dichloromethane and chloroform extracts were dried over anhydrous sodium sulfate or magnesium sulfate.

##### Phenylisothiocyanate (6).

Carbon bisulfide (12 g.) was added dropwise to a well stirred suspension of β-phenethylamine (20 g.) in a solution of 9 g. of potassium hydroxide in 40 ml. of water. The bright orange solution that was obtained was stirred for 10 minutes. Ethyl chloroformate (18 g.) was then added dropwise with stirring and cooling. Stirring was continued for another 0.5 hour; the reaction mixture was then extracted with dichloromethane and the organic layer was dried magnesium sulfate and evaporated to give crude **6**. The product on distillation afforded 15.5 g. of phenethylisothiocyanate (58%), b.p. 80-88°/1 mm (lit. (16) b.p. 95/0.5 mm). This sample was used for the next reaction without further purification.

Table 1  
Analytical and Spectral Data

Compound No.	M.p. °C	Yield %	Molecular Formula	Analysis			Spectral Data
				C	H	N	
<b>6</b>	B.P. 80-85	58	C <sub>9</sub> H <sub>9</sub> NS				Ir (neat): 2100, 2170, 1710 cm <sup>-1</sup>
<b>7</b>	96	80	C <sub>9</sub> H <sub>9</sub> NS				Ir (nujol): 3150 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 8.5 (t, 1H), 7.1-7.5 (m, 4H), 3.3-3.7 (m, 2H), 2.9-3.2 (t, 2H)
<b>9a</b>	96	55	C <sub>13</sub> H <sub>13</sub> NO <sub>2</sub> S	62.74 (62.64)	6.19 (6.07)		Ir (nujol): 1750 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.2-7.4 (m, 4H), 4.55 (s, 1H), 3.75 (s, 3H), 3.35-4.15 (m, 2H), 2.9-3.3 (m, 2H), 2.2 (s, 3H)
<b>9b</b>	145	58	C <sub>12</sub> H <sub>12</sub> N <sub>4</sub> OS	55.48 (55.38)	4.53 (4.65)	21.56 (21.53)	Ir (nujol): 1750 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.2-7.4 (m, 4H), 4.8 (s, 1H), 2.9-4.1 (m, 4H), 2.2 (s, 3H)
<b>9c</b>	oil	55	C <sub>13</sub> H <sub>12</sub> N <sub>4</sub> OS				Ir (neat): 3350, 1755 cm <sup>-1</sup>
<b>9d</b>	137	60	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> S	65.25 (65.21)	5.38 (5.47)	7.48 (7.60)	Ir (nujol): 3270, 1760, 1675 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 6.9-7.8 (m, 10H), 5.45 (d, 1H), 4.65 (s, 2H), 2.8-3.7 (m, 4H), 1.8 (s, 3H)
<b>9e</b>	133-134	69	C <sub>15</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	70.81 (70.79)	5.73 (5.63)	8.76 (8.69)	Ir (nujol): 3350, 1760, 1680 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.45-6.5 (m, 10H), 5.6 (q, 1H), 4.85 (d, 1H), 4.45 (s, 2H), 4.2-2.8 (m, 4H)
<b>15</b>	141	61					Nmr (deuteriochloroform): δ 7.45-8.2 (m, 4H), 5.6 (t, 1H), 3.75 (s, 3H), 3.6 (d, 2H), 3.35 (s, 3H)
<b>16a</b>	148	60	C <sub>20</sub> H <sub>19</sub> NO <sub>4</sub> S	64.98 (65.03)	5.12 (5.18)	3.89 (3.79)	Ir (nujol): 1770, 1750 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.35 (s, 9H), 5.42 (s, 1H), 4.5 (t, 1H), 3.85 (s, 3H), 3.3 (m, 2H), 2.5 (s, 3H)
<b>16b</b>	179	40	C <sub>15</sub> H <sub>17</sub> NO <sub>4</sub> S	58.80 (58.63)	5.68 (5.68)	4.75 (4.56)	Ir (nujol): 1765, 1740 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.35 (s, 4H), 4.65 (s, 1H), 4.5 (t, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.3 (m, 2H), 2.45 (s, 3H)
<b>16c</b>	134	60	C <sub>21</sub> H <sub>21</sub> NO <sub>4</sub> S	65.63 (65.79)	5.65 (5.59)	3.82 (3.65)	Ir (nujol): 1765, 1740 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.2-7.8 (m, 9H), 5.1 (s, 1H), 4.9 (t, 1H), 4.8 (s, 2H), 3.85 (s, 3H), 3.4 (m, 2H), 2.5 (s, 3H)
<b>16d</b>	156-158	55	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub> O <sub>3</sub> S	52.66 (52.83)	4.35 (4.43)	17.46 (17.60)	Ir (nujol): 2110, 1765, 1740 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.4 (s, 4H), 4.97 (s, 1H), 4.5 (t, 1H, J = 9 Hz), 3.85 (s, 3H), 3.35 (dd, 2H, J = 9 Hz), 2.4 (s, 3H)
<b>16e</b>	220	50	C <sub>19</sub> H <sub>17</sub> NO <sub>4</sub> S	63.96 (64.22)	4.79 (4.82)		Ir (nujol): 1760, 1725 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.3 (s, 9H), 5.45 (s, 1H), 4.4 (t, 1H), 3.3 (d, 2H), 2.45 (s, 3H)
<b>16f</b>	oil	60					Ir (nujol): 3350, 1765, 1735 cm <sup>-1</sup>
<b>16g</b>	163	50	C <sub>22</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub> S	62.16 (61.97)	5.30 (5.20)	6.64 (6.57)	Ir (nujol): 1771, 1750, 1685 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.8-7.0 (m, 10H), 5.6 (d, 1H), 4.70 (s, 2H), 4.45 (t, 1H), 3.85 (s, 3H), 3.30 (m, 2H), 1.95 (s, 3H); ms: M <sup>+</sup> at m/e 426.
<b>16h</b>	179-180	50	C <sub>21</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub> S				Ir (nujol): 3200, 1770, 1740, 1640 cm <sup>-1</sup> ; nmr (deuteriochloroform and DMSO-d <sub>6</sub> ): δ 7.0-8.4 (m, 10H), 5.6 (d, 1H), 5.25 (s, 2H), 4.75 (m, 1H), 3.45 (b, 2H), 2.0 (s, 3H); ms: M <sup>+</sup> + 1 at m/e 413 and M <sup>+</sup> + NH <sub>4</sub> at m/e 430 in CIMS.
<b>16i</b>	119-120	60	C <sub>21</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub>				Ir (nujol): 1740, 1720, 1620 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 6.6-7.4 (m, 10H), 5.57 (q, 1H), 5.0 (d, 1H), 4.5 (s, 2H), 4.15 (m, 1H), 3.9 (s, 3H), 3.3 (m, 2H); ms: M <sup>+</sup> + 1 at m/e 381 in CIMS.
<b>16j</b>	152-156	60	C <sub>20</sub> H <sub>18</sub> N <sub>2</sub> O <sub>5</sub>				Ir (nujol): 3250, 1760, 1740, 1640 cm <sup>-1</sup> ; ms: M + NH <sub>4</sub> <sup>+</sup> at m/e 384 in CIMS.

### 3,4-Dihydrothioisocarbostyryl (7).

To a solution of phenethylisothiocyanate (5 g.) in 50 ml. of dichloromethane was added 25 drops of concentrated sulfuric acid followed by 10 g. of aluminum chloride (anhydrous). The reaction mixture was refluxed

for 3 hours and poured into 200 ml. of an ice water mixture. The organic layer was separated and the aqueous phase was extracted with 100 ml. of dichloromethane. The combined dichloromethane extracts were dried and the solvent evaporated. The oily residue crystallised on standing to

give 11.0 g. (80%) of 3,4-dihydrothioisocarbostyryl. The product was recrystallized from dichloromethane-hexane, m.p. 98° (lit. (10) m.p. 98-99°).

#### 1-Methylthio-3,4-dihydroisoquinoline (8).

To 1 g. of 3,4-dihydrothioisocarbostyryl (7a) in 75 ml. of THF was added 1 g. of methyl iodide. The mixture was refluxed for 15 minutes when the product separated as the hydroiodide. The reaction mixture was cooled to room temperature and filtered to afford 1.4 g. (75%) of 8 hydroiodide, m.p. 195-198°. Using the same general conditions, the methyl thio derivative (15) was prepared in 61% yield from the carbostyryl (14) and methyl iodide.

#### General Synthesis of Octams.

To a solution of 1-methylthio-3,4-dihydroisoquinoline hydroiodide (8, 4 g.) in dichloromethane (125 ml.) were added dropwise 2.66 g. of triethylamine under anhydrous conditions. This was followed by dropwise addition of azidoacetyl chloride (1.55 g.) in dichloromethane. The mixture was stirred overnight at room temperature. The reaction mixture was washed with 5% hydrochloric acid (2 × 100 ml.), sodium bicarbonate (5%) and water. The organic layer was dried (magnesium sulfate) and evaporated. The residue was passed through a Florisil column and eluted with dichloromethane. Recrystallization of the product with ether afforded 2 g. (59%) of 9b m.p. 140-141° dec.

Using appropriate acid chlorides and dihydroisoquinolines, the octams 9a and 16a-16d were also prepared. The analytical and spectral data of these compounds are described in Table 1.

#### Reduction of Azido Octams.

The solution of the azido octam (9b, 3 g.) in 150 ml. of THF containing 0.6 g. of 10% palladium on carbon was hydrogenated at 40 psi for 20 hours. The catalyst was filtered and the solvent evaporated under reduced pressure. The product (9c) showed absence of azide band and the presence of amino function in its infrared spectrum and was used as such for the next reaction.

The azido  $\beta$ -lactam 16d was similarly reduced to 16f.

#### Acylation of Amino Octams.

To a THF (25 ml.) solution of 9c containing 1.28 g. of triethylamine were added dropwise a solution of 2.17 g. of phenoxyacetyl chloride in 25 ml. of THF. The mixture was stirred at room temperature for 2 hours filtered and the solvent evaporated. The oily residue was chromatographed using a Florisil column and dichloromethane as the eluent. The product was recrystallized (dichloromethane/ether) to give 2.0 g. of 9d, m.p. 134-135°.

The amino  $\beta$ -lactam 16f was similarly acylated to 16g.

#### Desulfurization of the Octams.

To a prewashed suspension of Raney nickel (10 g. in 5 ml. of acetone) was added 1 g. of 9d. The reaction mixture was refluxed for 7 hours and filtered. The catalyst was washed several times with acetone and dichloromethane. The combined washings and filtrate were dried (magnesium sulfate) and evaporated. The residue gave a solid product after trituration with ether which on crystallization from ether afforded 9e in 69% yield, m.p. 138°.

Using similar reaction conditions the octam 16g afforded the *cis* product 16i.

#### Synthesis of 3,4-Dihydro-3-carbomethoxythioisocarbostyryl (14).

The isocarbostyryl (13, 2 g., 0.01 mole) and phosphorus pentasulfide (0.88 g., 0.004 mole) were mixed intimately and suspended in 20 ml. of pyridine and placed in a preheated (140°) oil bath. Refluxing was continued with stirring for 2 hours. Thereafter the solution decanted into 50

ml. of water at room temperature. The solid product separated on trituration. The product was filtered and air dried to give 1.2 g. (50%) of thioisocarbostyryl (14), m.p. 155-157°.

#### Hydrolysis of Carbomethoxy Octams.

A stirred solution of the carbomethoxy octam 16a (200 mg.) in 10 ml. of water and 10 ml. of pyridine was cooled in ice-salt bath; 0.5 ml. of 1*N* sodium hydroxide was added and stirring was continued for 6 hours. The reaction mixture was then diluted with 25 ml. of water, layered with 20 ml. of ethyl acetate and acidified with concentrated hydrochloric acid (water layer pH 3, ethyl acetate layer pH 8). The ethyl acetate layer was separated. After washing in water, drying (magnesium sulfate) and evaporation of the solvent, 150 mg. of 16e, m.p. 215-216° (ether) were obtained.

Using similar reaction conditions the octams 16g and 16i were hydrolyzed to the acids 16h and 16j, respectively.

#### Acknowledgment.

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#### REFERENCES AND NOTES

- (1) Part LVI in the series Studies on Lactams. For part LV see A. K. Bose, M. S. Manhas, S. G. Amin, J. C. Kapur, J. Kreder, B. Ram and J. E. Vincent, *Tetrahedron Lett.*, 000 (1979).
- (2) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967).
- (3a) A. K. Bose and J. L. Fahey, *J. Org. Chem.*, **39**, 115 (1974); (b) A. K. Bose, J. L. Fahey and M. S. Manhas, *Tetrahedron*, **30**, 3 (1974); (c) J. L. Fahey, B. C. Lange, J. M. van der Veen, G. R. Young and A. K. Bose, *J. Chem. Soc., Perkins Trans. 1*, 1117 (1977).
- (4a) M. S. Manhas, B. Lal, S. G. Amin and A. K. Bose, *Synth. Commun.*, **6**, 435 (1976); (b) M. S. Manhas, S. G. Amin, H. P. S. Chawla and A. K. Bose, *J. Heterocyclic Chem.*, **15**, 601 (1978); (c) M. S. Manhas, S. G. Amin and R. D. Glazer, *ibid.*, **16**, 283 (1979).
- (5) R. N. Guthikonda, L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7584 (1974).
- (6) J. Finkelstein, K. G. Holden and C. D. Perchonock, *Tetrahedron Letters*, 1629 (1978).
- (7) A. K. Bose, B. Dayal, H. P. S. Chawla and M. S. Manhas, *ibid.*, 2823 (1972).
- (8) A. K. Bose, M. S. Manhas, J. S. Chib, H. P. S. Chawla and B. Dayal, *J. Org. Chem.*, **39**, 2877 (1974).
- (9) S. Wolfe and S. K. Hasan, *Chem. Commun.*, 833 (1970).
- (10) P. A. S. Smith and R. O. Kan, *J. Org. Chem.*, **29**, 2261 (1964).
- (11) Using similar reaction conditions  $\beta$ -phenylpropylamine could be converted to 4-methyl-1-methylthio-3,4-dihydroisoquinoline, m.p. 170-174°.
- (12) For details of this system of nomenclature see, A. K. Bose, *J. Heterocyclic Chem.*, **13**, 93 (1976).
- (13) G. E. Hein and C. Niemann, *J. Am. Chem. Soc.*, **84**, 4487 (1962).
- (14) A stock solution of the test compounds at a concentration of 2000  $\mu$ /ml. in a 0.05*M* phosphate buffer solution at pH 6.5 was prepared and twofold dilutions were made with sterile buffer. Then, 1-ml quantities of each dilution were then incorporated into 19 ml. of brain heart infusion agar in sterile petri dishes. The hardened surface was then inoculated with the test organisms and it was then incubated for 18 hours at 37°. The minimum inhibitory concentration (MIC) which is the least amount of compound completely inhibiting the test organism was determined in  $\mu$ /ml. The biological testing was kindly conducted by Gist-Brocades N.V., Netherlands.