CHAPTER - II

SYNTHESIS OF S - TRIAZINE CEPHALOSPORIS

EXPERIMENTAL:-

Introduction:- The development of semisynthetic penicillins began in the early 1960's following the isolation of penicillins and cephalosporin nuclei. The two series collectively known as "classical and non-classical" Beta lactams". Classical Beta-lactams increased in number dramatically over the following years by virtue of a host of side-chain agalogues. The changes in the side-chain as well as the type of bonding[1,2] alter, biological activity and mode of action of cephalosporins at 7B.

This research investigation reports the synthesis of Beta-lactam antibiotics; amino acid derivatives of 7- (6-chloro - 1, 3, 5, - trazine - 2 - ylamino) desacetoxycephalosporinic acid as shown in scheme.

Cyanuric chloride is used as base acceptor in antibiotic preparation[3] and as hydrochlorinating reagent for alcohols[4]. Cyanuric chloride clearly is to be classified as an acyl halide. Amino s-triazine reacts as amides and formation of amide is a stepwise reaction and sodium hydroxide is good acid acceptor[5].

EXPERIMENTAL:-

Reagents and solvents used in synthetic work were the commercial preparations, unless otherwise indicated. Chemicals were of reagent grade and were used without further purification.

Ultracryostatic equipment with temperature control was used for carrying out the experiments.

IR spectra (KBr/Nujol/$CHcl_3$) were recorded on Perkin Elmer - 783 spectrophotometer, melting points are uncorrected.

The synthesis of Beta-lactam antibiotics involves two steps - as.

(I) **Preparation of S-triazine Derivatives**

Various Amino Acis like Glutamic acid, Aspartic Acid, Alanine, Leucine and Lysine were allowed to react with cyanuric chloride to get monosubstituted derivatives of cyanuric chlorides lic.

Preparation of 2,4 chloro-6 Glutamilic, 1-3-5-triazine (2a)

To a stirred suspension of Glutamic acid 3.5 gm (30 m mol) in Acetone/water (80 : 20) v/v), sodium bi-carbonate 2.5 gm (30 m mol) is added slowly by maintaining the temperature between 0° - 5°C, to attain the PH 7 - 7.5 and the resulting solution was treated with cyanuric chloride (2) 5.6 g.(30 m mol) slowly in small

portions. The reaction mixture was stirred for 3 - 4 hours, 0° - 5°C. The sodium salt was decomposed by addition of dil HCL below 0° - 5°C, and the resulting product was filtered, washed with 25 ml acetone and dried at room temperature to give white crystalline product (3gm, 85.7%) m.p. 185°C, IR(KBR) carboxyl C=0 1705 - 1720 cm^{-1}, NH bending 1510 - 1540 cm^{-1}, $C_3N_3Cl_2$ - 850 cm^{-1} Elemental Analysis (%) claculated for $C_8H_8O_4N_4Cl_2$)) : C, 32.54, H, 2.71 ; cl, 24.0; N, 18.98; 0, 21.69.

Preparation of 2, 4 dichloro - 6 Asparate - 1, 3, 5 - triazine (2b) -

To stirred suspension of aspartic Acid 3 g (22 m mol) in Acetone/water (80 : 20 v/v), sodium bi-carbonatc 1.89 g (22 m mol) is slowly added by maintaining the temparature between 0 - 5°C, to attain the PH - 7 - 7.5, and the resulting sloution was treated with cyanuric chloride (2) 4.16 g (22 m mol) slowly in small portions. The reaction mixture was stired for 3 - 4 hours, at 0° - 5°C, The sodium salt of the product was decomposed by addition of dil HCL below 0 - 5°C, and the resulting product was filtered, washed with 25 ml acetone and dried at room temperature to give white crystalline product (2.5 gm, 83.3%) M.P. 220°C dec, IR(KBR) carboxyl C = 0 1680 - 1700 cm^{-1}, NH bending 1480 - 1510 cm^{-1}, $C_3N_3Cl_2$ - 840 cm^{-1}, Elemental Analysis(%) calculated for ($C_7H_7O_4N_4Cl_2$) ; C, 30 ; H, 2.5 ; Cl, 25.37; N, 19.28; 0, 22.85;

Preparation of 2 - alanino - 4,6 - dichloro - 1,3,5 - triazine (2C)

To a stirred suspension of Alanine 3.5 g (39 m mol) in Acetone / water (80 ; 20 v/v), sodium bi-carbonate 3.3 g (39 m mol) is slowly added by maintaining the temperature between 0 - 5°C, to attain the PH 7 - 7.5, and the resulting solution was treated with cyanyric chloride (2) 7.2 g (39 m mol) slowly in small portions. The reaction mixture was stirred for 3 - 4 hours, at 0 - 5°C, The sodium salt of the product was decomposed by addition of dil HCL below 0 - 5°C and the resulting product was filtered and washed with 25 ml. of Acetone and dried at room temperature to give white crystalline product (2 gm, 57%) M.P., 230°C dec, IR (KBr) carboxyl C = O 1700 - 1720 cm^{-1} , NH bending 1520 - 1560 cm^{-1}, $C_3N_3Cl_2$ - 790 cm^{-1} , Elemental Analysis (%) calculated for $C_6H_5N_4Cl_2O_2$)), C, 30·37 ; H, 2·53 ; Cl, 29·98 ; N, 23·62 ; O, 13·50

Preparation of 2 - Leusino - 4,6 - dichloro - 1,3,5 - triazine (2 d) :

To a stirred suspension of Leusine 3 g (22 m mol) in Acetone/Water (80 : 20 v/v), sodium bi-carbonate 1.923 g (22 m mol) is added slowly by maintaining the temperature between 0 - 5°C, to attain the PH 7 - 7.5, and the resulting solution was treated with cyanuric chloride (2) 4.225 g (22 m mol) slowly in small portions. The reaction mixture was stirred for 3 - 4 hours, at 0 - 5°C. The sodium salt of the product was decomposed by addition was filtered and washed

with 25 ml acetone and dried at room temperature to give white crystalline product (1.89g , 63 %) M.P. 210°C dec, IR (KBr) carboxyl C = O 1630 - 1680 cm^{-1} , NH bending 1500 - 1540 cm^{-1}, $C_3N_3Cl_2$ 800 cm^{-1} , Elemental, Analysis (%) calculated for ($C_9H_{12}O_2N_4Cl_2$); C, 38.70; H, 4.30; Cl, 25.47; N, 20.07; O, 11.46.

Preparation of 2 - Lysino - 4,6 - di chloro - 1,3,5 - triazine (2 e)

To a stirred suspension of Lysine 3 g (20.5 m. mol) in Acetone / water (80 : 20 v/v), sodium bicarbonate 1.72 gm (20.5 m mol) is added slowly by maintaining the temperature between - 0 - 5°C, to attain the PH 7 - 7.5 , and the resulting solution was treated with cyanuric chloride 3.78 g (20.5 m mole) slowly in small portions. The reaction mixture was stirred for 3 - 4 hours, at 0 - 5°C, the sodium salt of the product was decomposed by addition of dil HCL at 0 - 5°C, and the resulting product was filtered and washed with 25 ml Acetone and dried at room temperature to give white crystalline product (2.6 g, 86.6%) M.P. above 182°c dec., IR (KBr) carboxyl C = O - 1680 - 1700 cm^{-1}, NH bending 1500 - 1530 cm^{-1}, $C_3N_3Cl_2$ - 800 cm^{-1} Elemented Analysis (%) calculated for ($C_9H_{13}O_2N_5Cl_2$) ; C, 36.73 H, 4.42; cl, 24.17; N, 23.80; O, 10.88.

(II) **Preparation of s - triazine Cephalospcrins**:-

The monosubstitued derivatives of cyanuric chloride was made to react with 7 - Acetyl desacetoxy cephalosporanoic acid (7 ADCA) to get 7 - substituted Beta lactam antibiotics.

To a stirred suspension of 7 - ADCA 4 g (18.6 m.mol)(3) in Acetone / water (30 : 70 v/v), sodium bicarbonate 1.57 g (18.6 mole) is added slowly by maintaining the temperature between 0 - 5° to attain the PH 7 - 7.5 and the resulting solution was treated with monosubstituted cyanuric chloride deviratives in equimolecular was stirred for 6 - 7 hours at temperature, the sodium salt of resulting product was decomposed by addition of dil HCl below 0 - 5°C, and the resulting product was extracted with several portions of ethyl acetate. The solvent on evaporation gives pale brown coloured products.

Preparation of 7-(6 - chloro - 4 - Glutamilic 1,3,5 - triazine - 2 -yl) ADCA

Weight of the product formed was 1.2 g (30%) with Melting Analysis (%) calculated for ($C_{16}H_{17}O_7N_6S$ Cl) :
C, 40.63, H, 3.59, Cl, 7.52, N, 17.77, 0, 23.71, S, 6.78.
IR(KBr) Carboxyl C=O 1590 cm^{-1}, NH bending 1730 cm^{-1}, β-lactam - 1400 cm^{-1}

Preparation of 7 - (6-Chloro-4-Asparate -1,3,5-triazine-2-yl) ADCA

Weight of the product formed was 0.750 g (18.7%) with Melting point 205°C dec., IR (KBr) carboxyl C=O 1600 cm^{-1}, NH bending 1720 - 1750 cm^{-1}, Beta-lactam, 1400 - 1440 cm^{-1}, C_3N_3Cl, 850 cm^{-1}
Element Analysis (%) calculated for ($C_{15}H_{15}O_7N_6SCl$) ( )
C, 39.18; H, 3.48; Cl, 7.73; N, 18.28; 0, 24.37; S, 6.96

Preparation of 7-(6-Chloro-4-Alanino-1,3,5-triazine-2-yl)ADCA

Weight of the product formed was 1.2 g (30%), with Melting point 252°C dec, IR (KBr) Carboxyl C = 0 1580 - 1620 cm^{-1},

, NH bending 1500 - 1520 cm^{-1} Beta-lactam 1795 cm^{-1}, C_3N_3Cl 795 cm^{-1} . Elemental Analysis (%) claculated for ($C_{14}H_{15}O_5N_6SCl$) ; C, 40.53; H, 3.61; Cl; 8.56; N, 20.26; O, 19.31; S, 7.73.

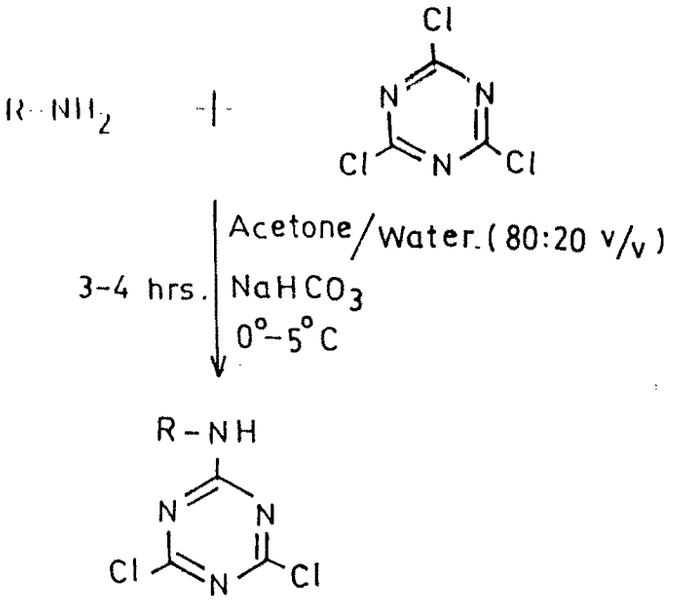
Preparation of 7-(6-Chloro-4-Leusino-1,3,5-triazin-2-yl) ADCA (3d)

Weight of the Product formed was 0.920 g (23%), with Melting point 220°C dec., IR (KBr) carboxyl C = O 1700-1720 cm^{-1} NH bending 1510-1540 cm^{-1}, Beta-lactam 1800 cm^{-1} , C_3N_3Cl 795 cm^{-1} , Elemental Analysis (%) calculated for ($C_{17}H_{21}O_5N_6S$ Cl) ; C, 44.68; H, 4.61 ; Cl, 7.77; N, 18.41; O, 17.52; S, 7.01.

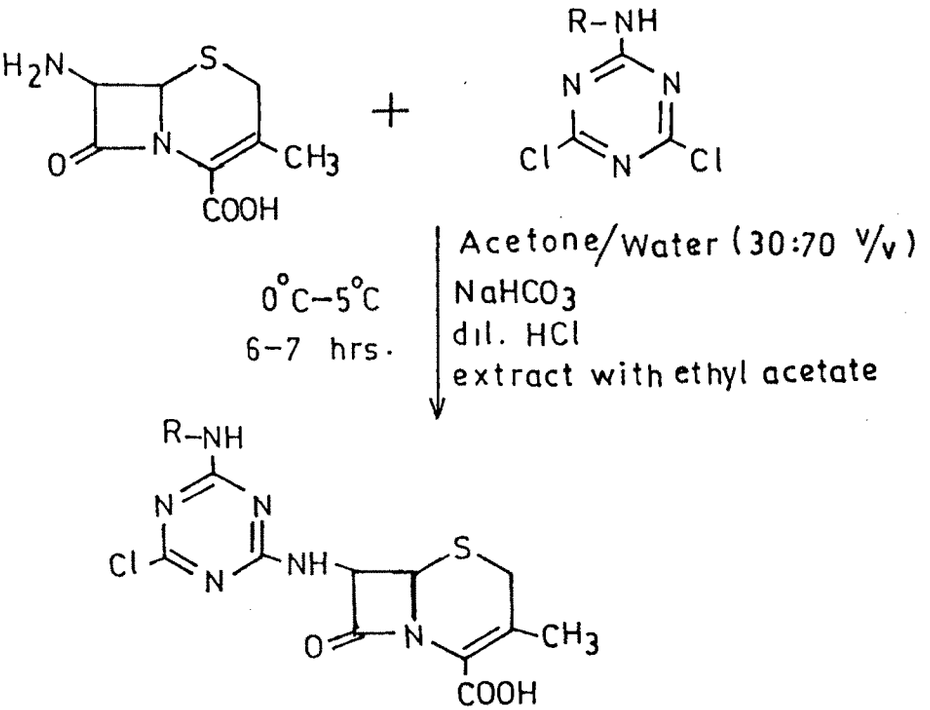
Preparation of 7-(6-Chloro-4-Lysino-1,3,5-triazin-2-yl) ADCA (3 e)

Weight of the product formed was 1.5 gm (37.5%), with Melting point 190°C dec., IR (KBr) carboxyl C =O 1720 cm^{-1} NH bending 1520-1550 cm^{-1}, Beta-lactam 1800 cm^{-1} , C_3N_3Cl - 810 cm^{-1} . Analysis calculated for ($C_{17}H_{22}O_5$ C, 43.27; H, 4.67; Cl, 7.53, N, 20.78, O, 16.97; S, 6.78

SCHEME–I



SCHEME–II



Where R =

1) $HOOC\ CH_2\ CH_2\ \underset{\displaystyle COOH}{\underset{|}{CH}}-$ Glutamic acid

2) $HOOC-CH_2-\underset{\displaystyle COOH}{\underset{|}{CH}}-$ L. Aspartic acid

3) $(CH_3)_2-CH-CH_2-\underset{\displaystyle COOH}{\underset{|}{CH}}-$ L (Lemine)

4) $H_2N-(CH_2)_4-\underset{\displaystyle COOH}{\underset{|}{CH}}-$ L (Lysine)

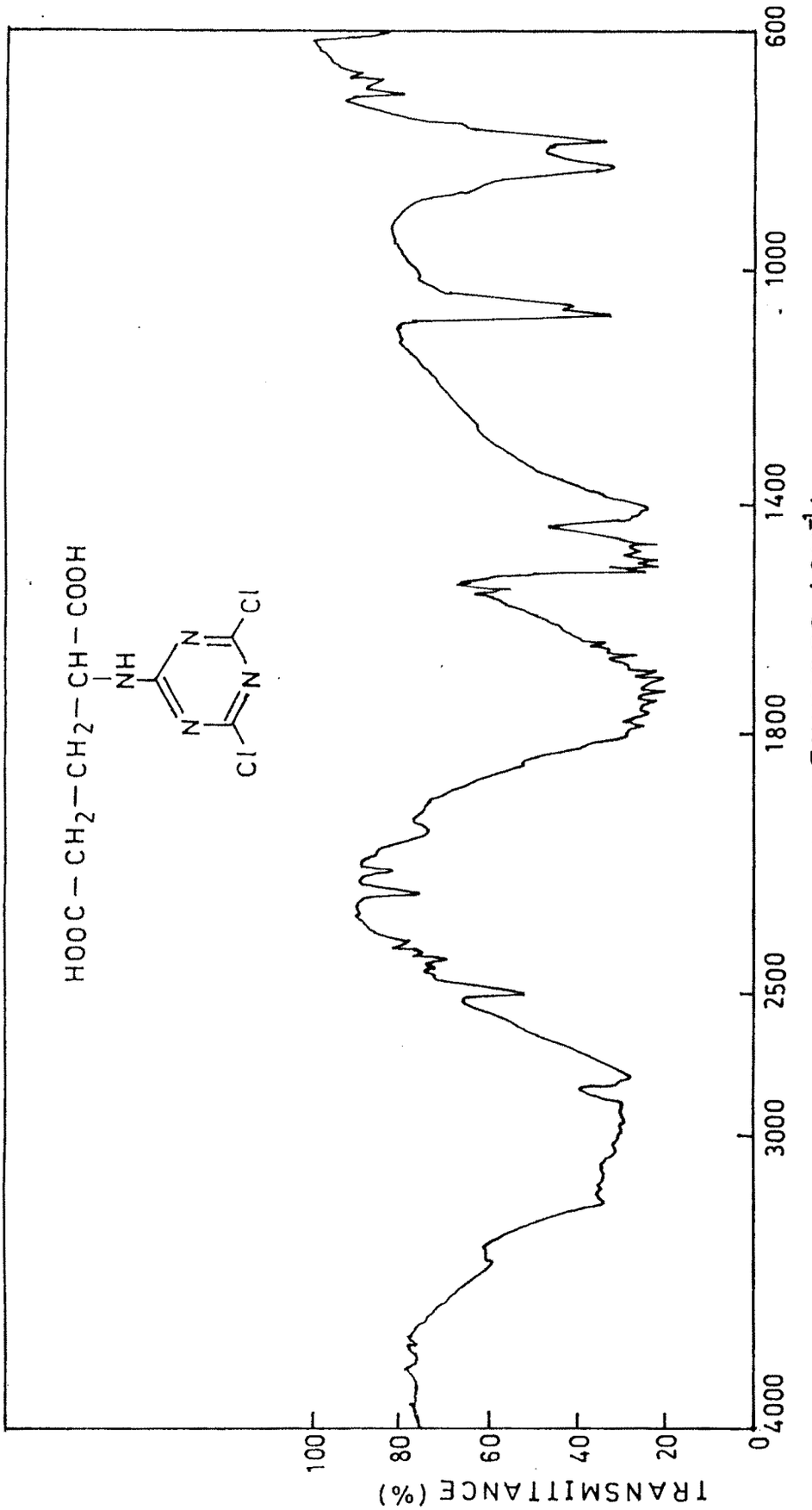

HOOC — CH2 — CH2 — CH — COOH
NH
N
N
N
Cl
Cl
TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2500
1800
1400
1000
600
WAVENUMBER (CM-1)

FIG.

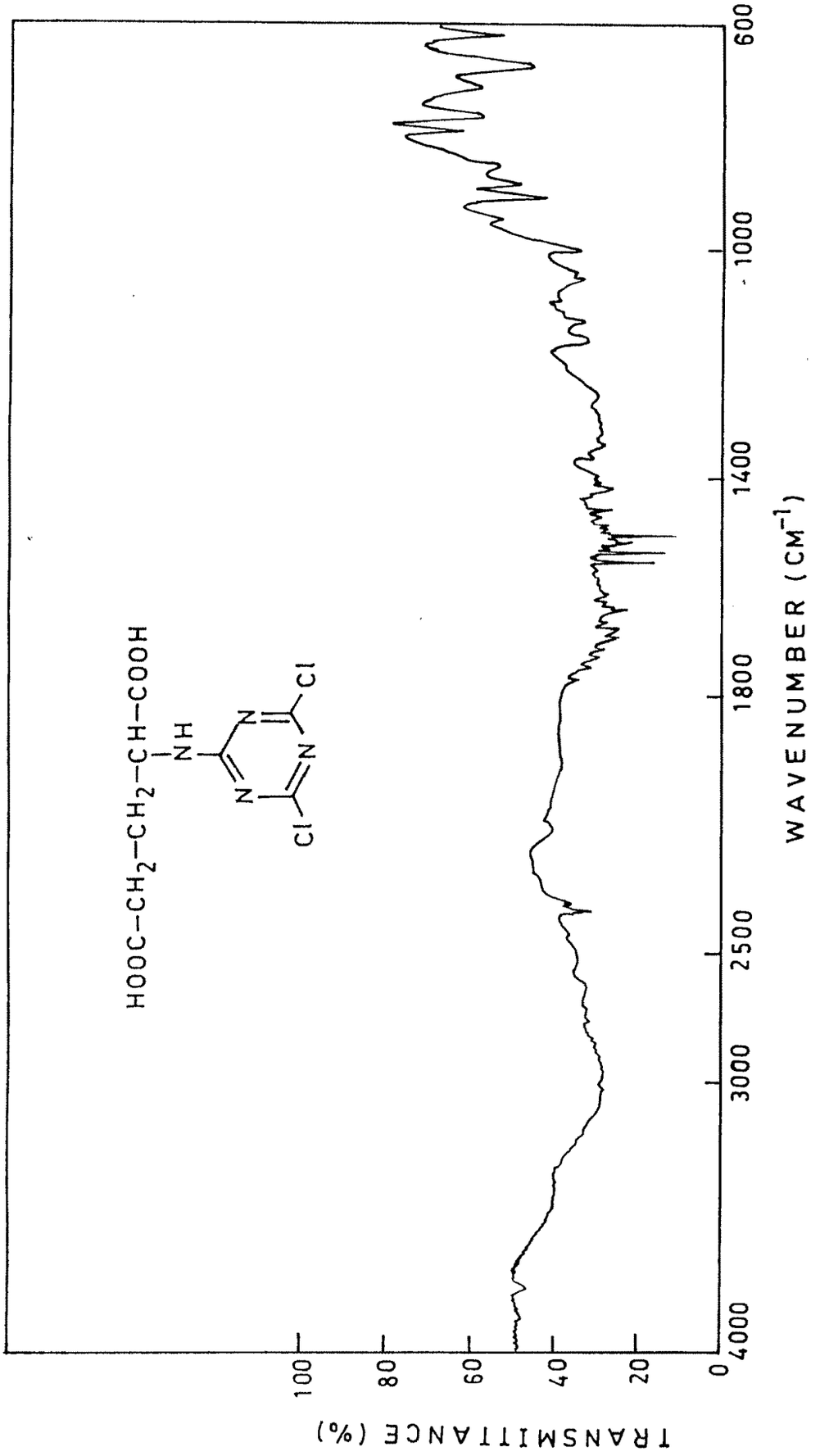

TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2500
1800
1400
1000
600
WAVENUMBER (CM⁻¹)
HOOC—CH₂—CH₂—CH—COOH
NH
N
N
Cl
Cl

FIG.

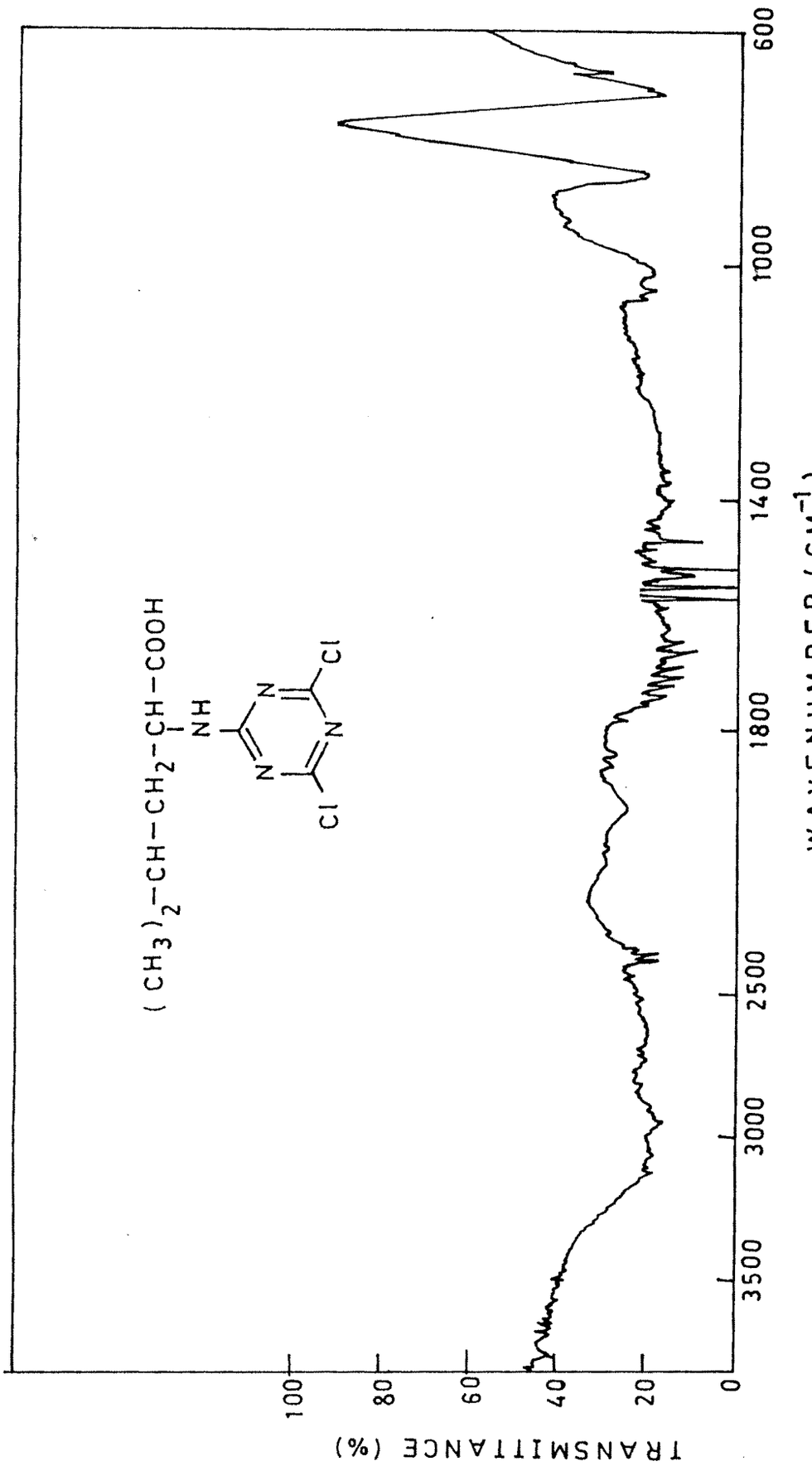

TRANSMITTANCE (%)
100
80
60
40
20
0
3500
3000
2500
1800
1400
1000
600
WAVENUMBER (CM^{-1})
$(CH_3)_2-CH-CH_2-CH-COOH$
NH
N
N
N
Cl
Cl

FIG.

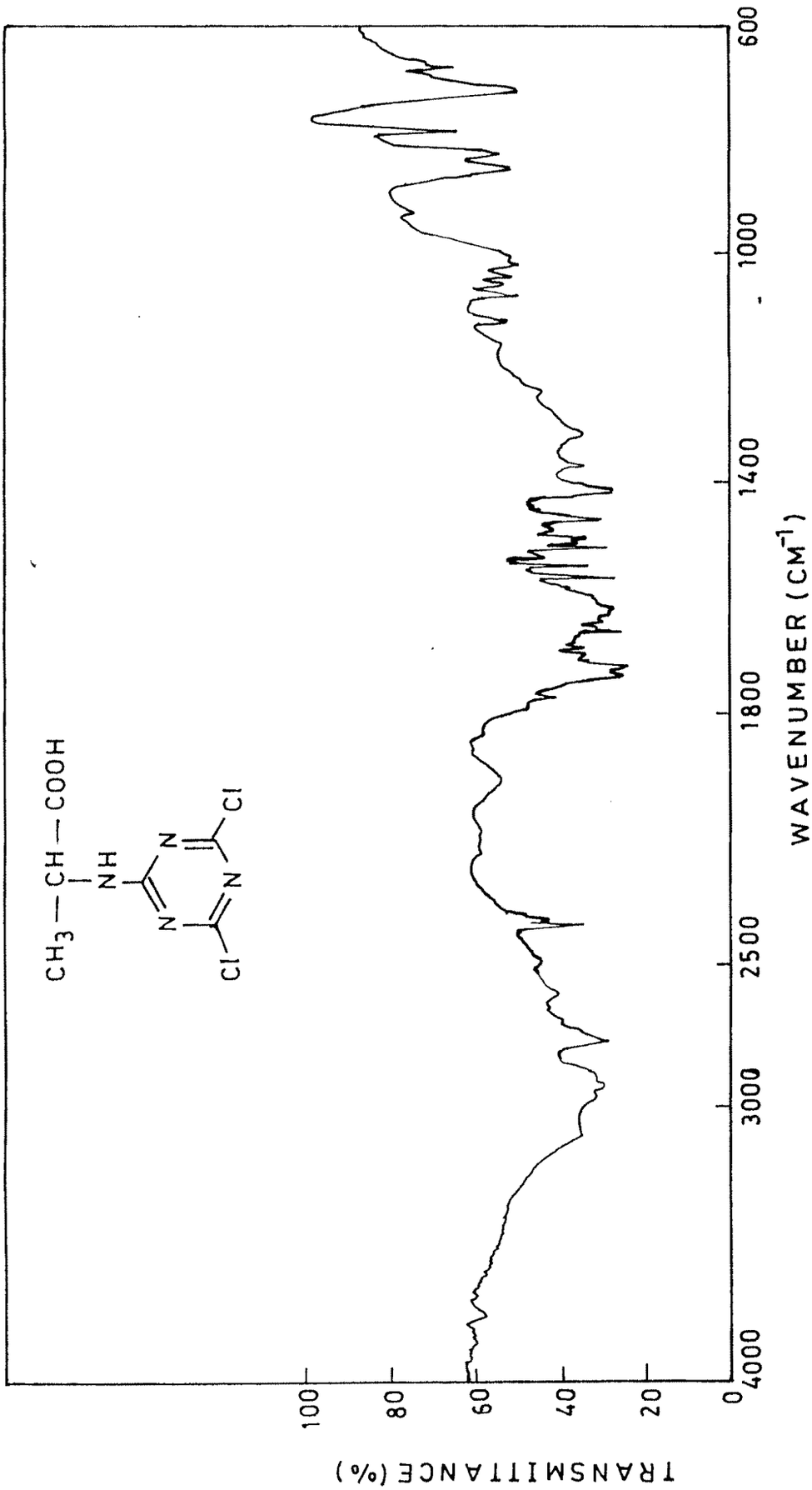

TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2500
1800
1400
1000
600
WAVENUMBER (CM⁻¹)
CH3—CH—COOH
NH
N
N
N
Cl
Cl

FIG.

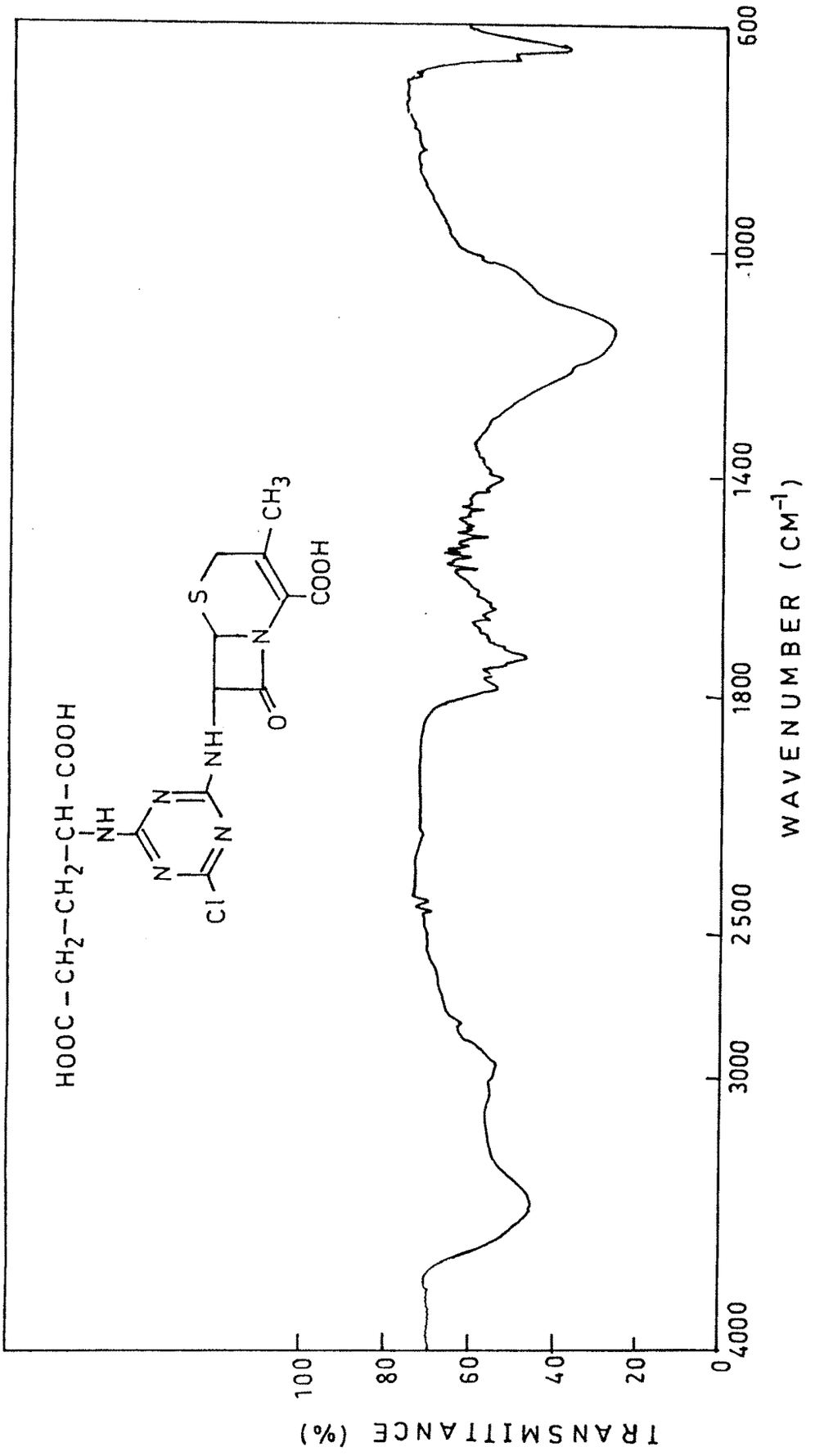

HOOC-CH2-CH2-CH-COOH
NH
N
N
Cl
NH
O
S
N
COOH
CH3
TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2500
1800
1400
1000
600
WAVENUMBER (CM-1)

FIG.

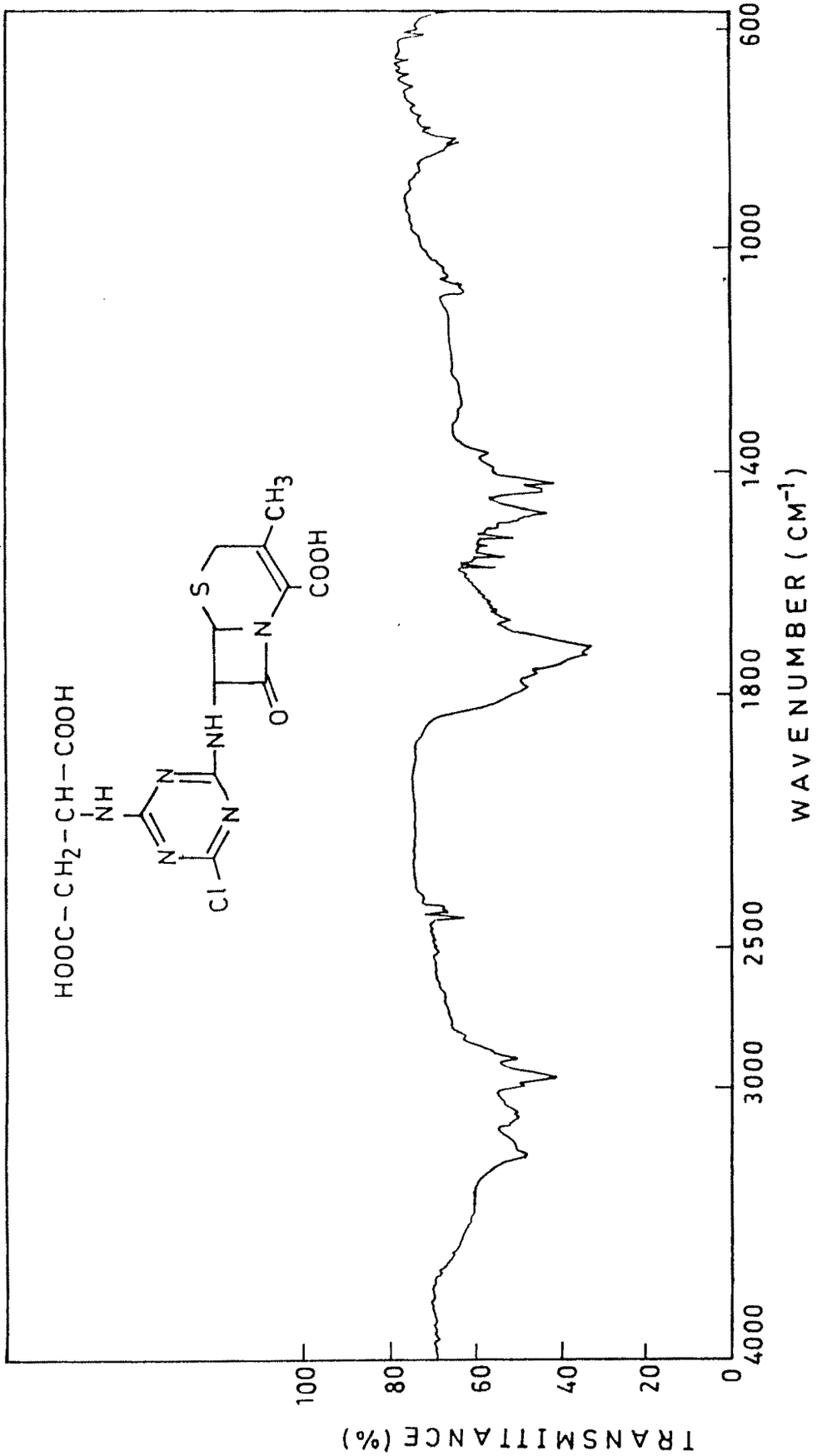

TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2500
1800
1400
1000
600
WAVENUMBER (CM⁻¹)
HOOC–CH₂–CH–COOH
NH
N
N
Cl
NH
O
N
S
CH₃
COOH

FIG.

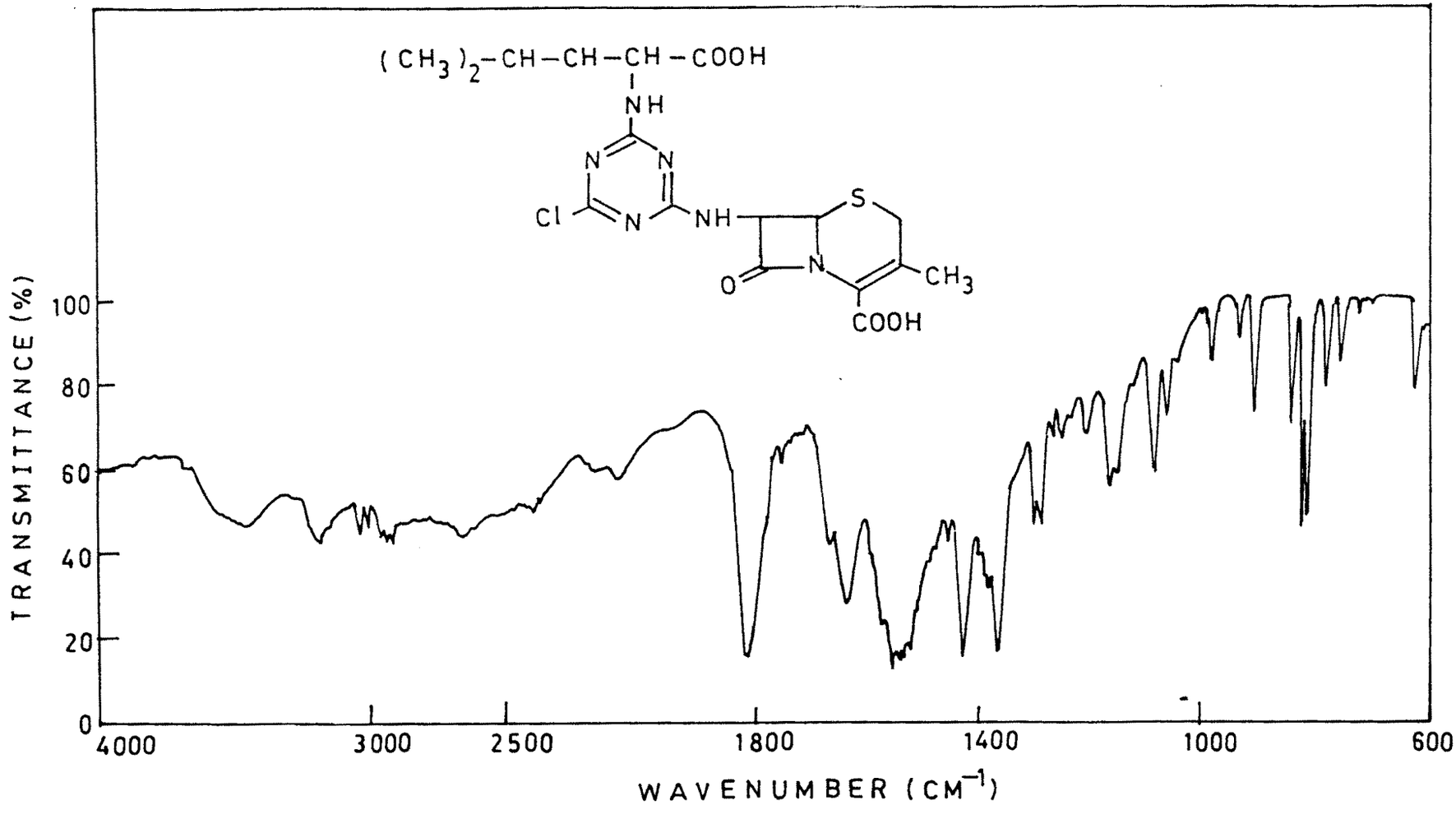

(CH3)2-CH-CH-CH-COOH
NH
N
N
Cl
N
NH
S
N
O
CH3
COOH
TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2500
1800
1400
1000
600
WAVENUMBER (CM-1)

FIG.

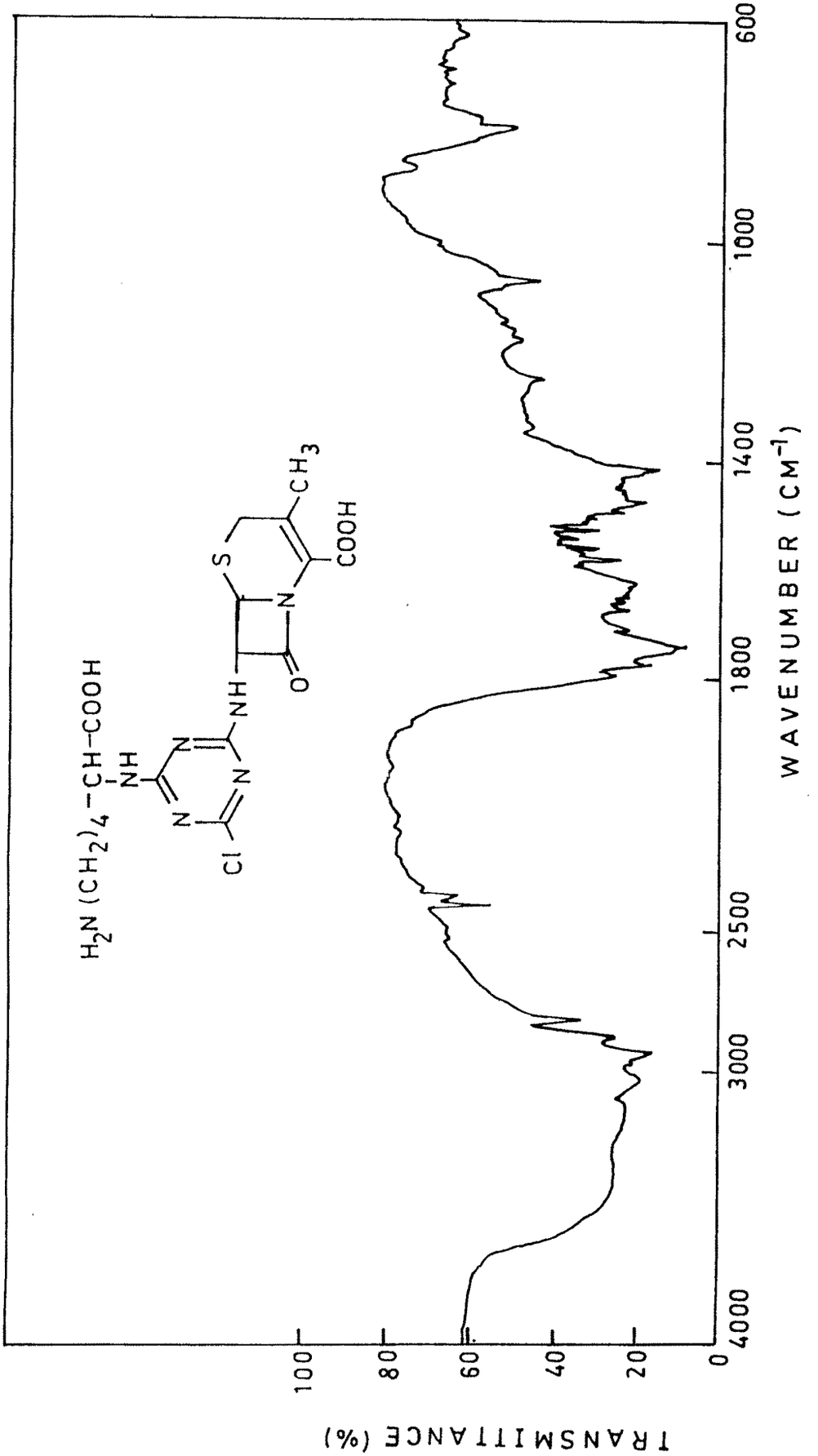

TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2500
1800
1400
1000
600
WAVENUMBER (CM⁻¹)
H2N(CH2)4-CH-COOH
NH
N
N
Cl
NH
S
N
O
CH3
COOH

FIG.

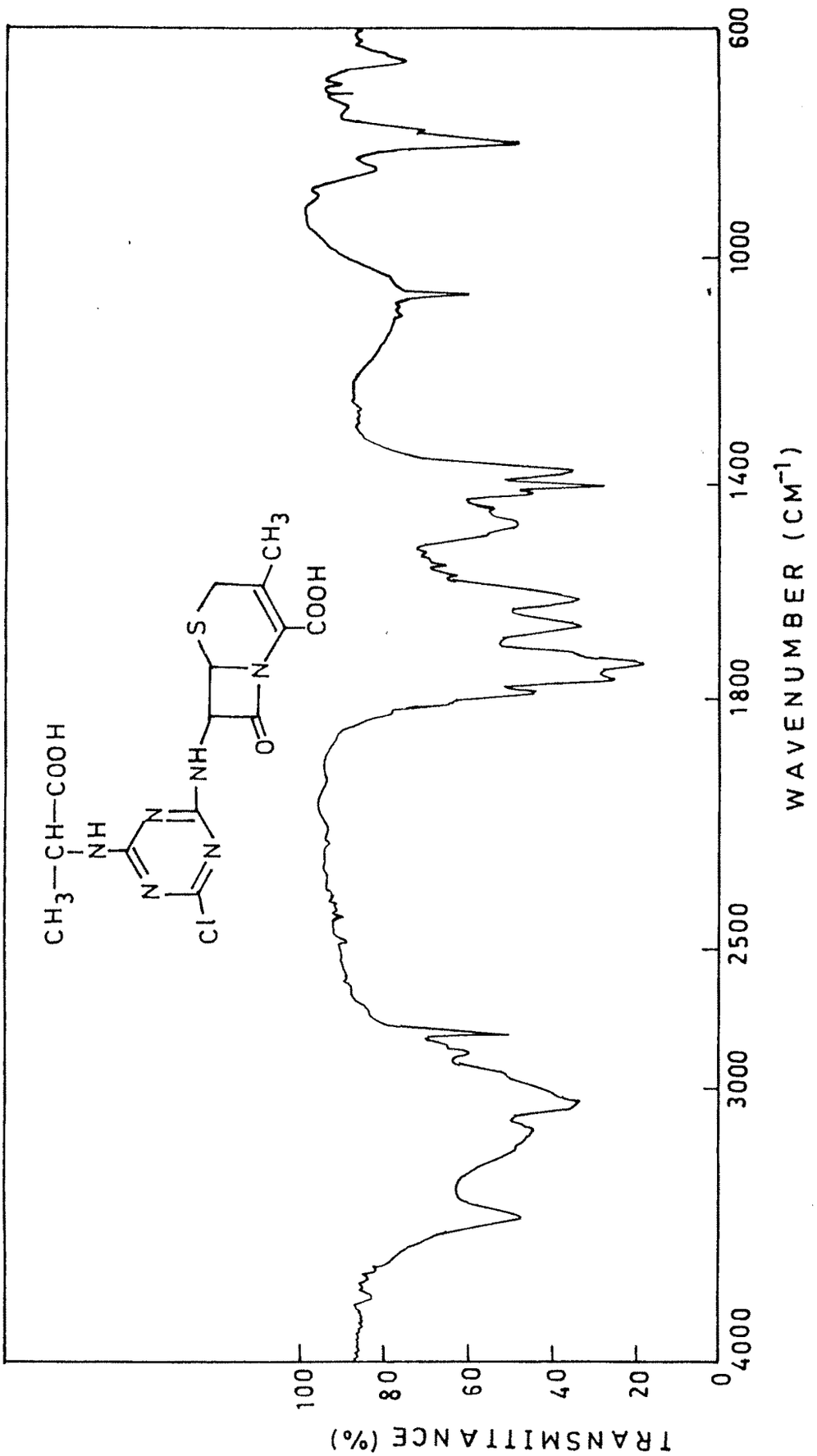

TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2500
1800
1400
1000
600
WAVENUMBER (CM⁻¹)
CH3—CH—COOH
NH
N
N
Cl
NH
O
N
S
CH3
COOH

FIG.

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