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SYNTHESIS OF 3-CARBOXYLIC DERVATIVES OF 1, 5-BENZOTHIAZEPINES

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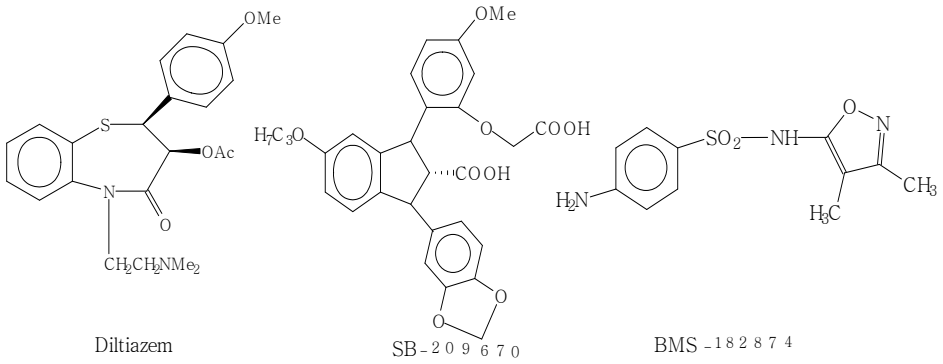
ABSTRACT

A series of 3- carboxylic derivaties of mono substituted 1,5-bensothiazepines(5-17) : 5-benzyl -4-oxo -2-phenyl - 2,3,4,5 – tetrahydro -1,5 -benzothiazepine-3- ethylcarboxylate (5), 5-(2- nitro benzyl) -4- oxo- 2- phenyl -2,3,4,5- tetra hydor- 1,5 - benzothiazepine - 3- ethyl carboxylate (6), 5-(3- nitro benzyl) -4- oxo- 2- phenyl -2,3,4,5- tetra hydor- 1,5- benzothiazepine -3- ethyl carboxylate (7), 5- (4- nitro benzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine - 3- ethyl carboxylate (8), 5- (2- methyl benzyl) -4-oxo-2- phenyl - 2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (9), 5- (3- methyl benzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (10), 5- (4- methyl benzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (11), 5- (2-bromobenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (12), 5- (3- bromobenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5-benzothiazepine -3- ethyl carboxylate (13), 5- (4- bromobenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (14) , 5- (3- methoxybenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (15), 5- (3,5-dimethoxybenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (16) and 5- (2,6- dichlorobenzyl) -4-oxo-2- phenyl - 2,3,4,5 - tetra hydro -1,5-benzothiazepine -3- ethyl carboxylate (17), was synthesized by hetrocyclisation from mercaptoaniline(1) with diethylebenzal malonate(2) followed by Nbenzylation of the heterocyle gave the derivatives of 4-oxo-2-phenyl 2,3,4,5-tetrahydro - 1,5- benzothiazepine.

KEYWORDS: Benzothiazepine, Endothelin Antagonist, Diltiazem, Synthesis.

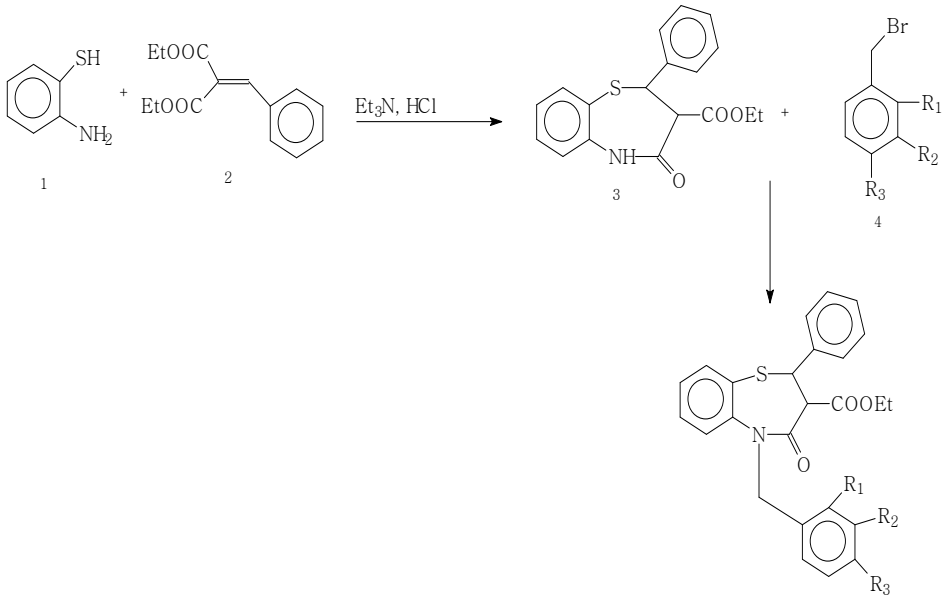
INTRODUCTION

Calcium channel blocker as diltiazem[1-3] and endothelin antagonists namely SB – 209670[4-6] and BMS – 182874 are protective cardiovascular agent by coronary vasodilatation and activation of coronary blood flow[7-12] (chart 1). Comparison of their structures prompted us to design novel protective agents with a mixed structure.



We wish to describe herein the synthesis of 3- carboxylic derivatives of monobenzyl substituted 1,5 - benzothiazepines which at present are being tested for their coronary vasodilator properties. Among thousands of benzothiazepinic compounds, those bearing a carboxylic group or derived moiety are very few. and none bearing carboxylic group at the 3-position is described.

The 1,5- benzothiazepines heterocycle was constructed in a one pot operation from 2-mercaptoaniline (1) by cyclization with diethyl benzalmalonate (2) **(chart 2).**



The carboxylic or the ester group in the 3-position of 1,5- benzothiazepine compounds could be introduced during the construction of the heterocyclic moiety to give the corresponding monocarboxylic acid or ester derivative.

The preparation of N-benzyl-3-carboxylic derivatives of 4-oxo-2-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepine (4) was achieved by cyclization of 2-mercaptaaniline (1) with diethyl benzalmalanate(2)which afforded ethyl ester of (4- oxo- 2- phenyl- 2,3,4,5- tetrahydro - 1,5-benzothiazepine-3-yl) carboxylic acid (4) .

The substituted benzyl group in the 5-position of 1,5 -benzothiazepine compounds could be introduced by benzylation reaction by different conditions.

MATERIALS AND METHODS

Melting points were determined with a Buchi 510 capillary apparatus and are uncorrected . Their spectra were recorded on a unicam SP 1100 infrared spectrophotometer using potassium bromide plates for solid products . The Frequencies are expressed in cm^{-1} . ^{1}H and ^{13}C- nmr spectra were obtained on a Bruker A C 200 spectrometer in deuteriochloro form or dimethylsulfoxide - d_6 solution . Chemical shifts are given in δ(ppm) units relative to the internal reference tetramethylsilane. The abbreviations of signal patterns are as follows :s: singlet, d:doublet,t: triplet, q: quartet , m: multiplet ,br: broad. Elemental analyses (C,H,N,Br,O, S, Cl) were carried out in the Service Central d'Analyses, Center National de la Recherche Scientifique, 69390 Vernaison ,France and were within±0,4 % of theoretical values unless otherwise noted .Reaction Progress and purity of products were checked by carrying out tlc using silica gel Merck 60 F 254; the spots were visualised by uv and iodine vapour.

RESULTS AND DISCUSSION

4- oxo- 2- phenyl – 2,3,4,5-tetrahydro- 1.5- benzothiazepine -3- ethyl carboxylat (3)[13]

A mixture of 2-mercaptoaniline (1) (6,3g ,50 mmoles),diethylebenzalmalonate (2) (12,4g, 50 mmoles)and triethylaminechlorhydrate (3g , 21,5 mmoles)was heated at 160° for 7 hours. After cooling to room temperature , ether was added . The crude product was filtered , dried to give 3g (18%) of 4- oxo- 2- phenyl - 2,3,4,5 -tetra hydro- 1,5 -benzothiazepine -3 - ethyl carboxylate (3),mp 176° ; ^{1}H nmr (DMSO-d_6) :δ1,24 (t ,3H ,CH_3 ,J= 7,2 Hz) , 4,18(m , 2H, CH_2 , J = 7,2 Hz) , 4,19 (d, 1H, CH, J=11,2Hz) , 5,29 (d, 1H ,CH, J =11,2Hz) , 7 -7,33 (m,7H , 6,8H,Phenyl protons),7.47(d,1H,CH,J=7,8 Hz),7,65(t,1H,CH, J= 7.5

Hz);IR(potassium bromide):700(C-S),1665(C=O amide),1755(C=O ester), 3070 – 3100(-NH-)cm^{-1}.

5-benzyl -4-oxo -2-phenyl - 2,3,4,5 – tetrahydro -1,5 -benzothiazepine-3-ethylcarboxylate (5)[14]

Potassium carbonate (0.35g, 2,5 mmoles) was added at 0˚ under nitrogen atmosphere to solution of 4-oxo-2- phenyl-2,3,4,5- tetrahydro-1,5-benzothiazepine -3- ethyl carboxylate(3) (0.83 g,2.5 mmoles)in dimethylformamide (4 ml) for 15 minutes, and at 25˚ for 10 minutes . Solution of benzyle bromide (4)(0.43g, 2.5 mmoles) in dimethylformamide (0,7 ml) was added to 0˚ and agitated at 25˚ for 20 minutes. After addition of 8 ml of saturated ammonium chloride solution in water, the mixture was extracted by ethyl acetate. The organic phase was washed with saturated sodium chloride solution, the collected extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column with chloroform and recrystallized from dry ethyl acetate: petroleum ether(2:8; v/v) to get 0.49 g (60%),mp143˚;^{1}H NMR(deuterio chloroform):δ 1.12 (t,3H, CH_3,J=7.11 Hz), 4.04 (d,1H, CH, J=12 Hz), 4.07(q,2H, CH_2 , J= 7.1 Hz), 5.06 (d,1H, CH, J= 12Hz),5.13(dd,2H,CH_2,J=15.2 Hz), 7.02-7.06(m, 2H,O-phenyl protons),7.21-7.30(m,9H, benzyl protons, benzo protons), 7.40-7.49 (m, 3H, p-phenyl protons). IR (potassium bromide):700(C-S), 1690 (C=O ester), 1750 (C=O amide)cm^{-1}.

Anal. Calcd for $C_{25}H_{23}NO_3S$:C,71.92; H,5.55; N,3.35; S,7.68. Found: C, 71.16; H,5.55; N,3.37;S,7.50.

5-(2- nitro benzyl) -4- oxo- 2- phenyl -2,3,4,5- tetra hydor- 1,5 - benzothiazepine -3- ethyl carboxylate (6).

A mixture of 4- oxo - 2- phenyl -2,3,4,5 - tetra hydor – 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g, 3 mmoles) and 2-nitrobenzyl bromide (0.64g, 4mmole) was dissolved in distilled THF (25ml). After addition of potassium hydroxide (0.17 g, 3mmol), the mixture was agitated at room temperature for 2 hours. The suspension was filtered, evaporated. The crude product was chromatographed on a silica gel column with chloroform to get 0.5g (50%) of 5-(2-nitrobenzyl) -4-oxo-2- phenyl- 2,3,4,5- tetra hydro- 1,5- benzothiazepine -3-ethyl carboxylate (6), mp 178^0; ^{1}H nmr (deuteriochloroform): δ 1.0 (t, 3H, CH_3, J= 7.2 Hz) 4.03 (m, 2H,CH_2) 4.10 (d, 1H, CH, J= 15.0 Hz) 5.05 (d, 1H, CH, J=12.0) 5.40 (d, 1H, CH, benzyl, J=15.0 Hz) 5.68 (d,1H,CH_2 benzyl, J=15.0 Hz) 7.03- 7.27 (m, 9H, benzo protons , phenyl protons), 7.45 (dt, 1H, P- benzyl protons , J=8.1, 7.6, 1.4 Hz), 7,61 (dt, 1H, m- benzyl

protons , J=7.6, 1.2 Hz), 7.86 (dd,1H, O- benzyl protons, J= 7.6 Hz), 8.01 (dd, 1H, m, benzyl protons, J=8.1 , 1.2 Hz); ir (potassium bromide): 700 (C-S) , 1525 (NO2), 1675 (C= o ester), 1745 (C=0 amide) cm -1.

Anal . Calcd for C_{25} H_{22} N_2 O_5S : C, 64.92 ; H, 4.79; N, 6.06, S, 6.93 . Found: C, 65.06, H, 4.74; N, 6.06; S,7.01.

5-(3- nitro benzyl) -4- oxo- 2- phenyl -2,3,4,5- tetra hydor- 1,5- benzothiazepine -3- ethyl carboxylate (7)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl – 2,3,4,5 – tetra hydro – 1,5-benzothiazepine -3- ethyl carboxylate (3) (1g , 3 mmoles) and 3- nitro benzyl bromide (0.64 g , 3 mmoles) and potassium hydroxide (0,17 g ,3 mmoles) . Obtained 0,3 g (30%) of 5- (3-nitro benzyl) -4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (7), mp 163° ; ^{1}H nmr (deuteriochloro form) : δ 1.10 (t , 3H , CH_3, J = 7.1 Hz), 4.02 (d, 1H, CH, J = 12.0Hz) , 4.05 (m, 2H, CH_2) , 5.00 (d, 1H ,CH_2 benzyl , J = 15.4 Hz), 5.04 (d, 1H, CH, J = 12.0Hz) , 5.41 (d , 1H, CH_2 benzyl , J = 15.4 Hz) , 6.98 - 7.03 (m, 2H, 6, 7 H), 7.19 - 7.30 (m, 6H, 8,9 H , phenyl protons), 7.45 (t,1H, m-benzyl, J =7.7 Hz) , 7.50-7.53 (m, 1H, m- phenyl) ,7.71 (dd, 1H, o- benzyl , J = 7.7 Hz) , 8.09 (dd , 1H, p- benzyl , J = 7.7 Hz) , 8. 12 (S, 1H, o-benzyl) ; ir (potassium bromide) : 700 (C-S) , 1525 (NO_2) , 1675 (C = O ester) , 1750 (C = O amide) cm $^{-1}$.

Anal . Calcd for C_{25} H_{22} N_2 O_5 S : C, 64.92 ; H, 4.79 ; N, 6.06 ; S , 6.93 . Found, C , 65.20; H, 4.80 ; N , 6.03 ; S , 7.12.

5- (4- nitro benzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (8)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5-benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 4- nitro benzyl bromide (0,64 g, 3 mmoles) and potassium hydroxide (0,17 g ,3 mmoles) . 0,3 g (30%) was Obtained of 5-(4-nitro benzyl)-4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (8), mp 188° ; ^{1}H nmr (deuteriochloroform): δ 1.10 (t,3H , CH3 , J = 7.1 Hz) , 4.02 (d , 1H , CH , J = 11.9 Hz) , 4.05 (m , 2H , CH_2) , 5.00 (d , 1H , CH_2 benzyl , J = 15.5 Hz), 5.03 (d, 1H , CH, J = 11.9 Hz) , 5.41 (d , 1H , CH_2 benzyl , J = 15.5 Hz) , 7.00 - 7.03 (m, 2H , 6, 8 H) , 7.21 - 7.50 (m, 7H ,7,9 H, phenyl protons) , 7.49 (dd, 2H ,o- benzyl , J = 8.7 Hz),

8.11 (dd , 2H, m - benzyl , J = 8.7 Hz); ir (potassium bromide) : 700 (C-S) , 1515 (NO_2) , 1660 (C=O ester) , 1750 (C=O amide) cm^{-1}.

Anal. Calcd for C_{25} H_{22} N_2 O_5 S: C, 64. 92; H, 4.79; N, 6.06; S, 6.93. Found : C, 65.11; H, 4.80; N, 6.03 ; S, 7.07.

5- (2- methyl benzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (9)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 2- methyl benzyl bromide (0,55 g , 3 mmoles) and potassium hydroxide (0,17 g ,3 mmoles) . 0,15 g (15%) was Obtained of 5- (2-methyl benzyl) -4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (9) , mp 116° ; 1H nmr (deuteriochloroform): δ 1.13 (t,3H , CH3 , J = 7.1 Hz) , 2,34 (S , 3H , CH_3 benzyl) , 4.06 (m , 2H ,COO CH_2) , 4.15 (d , 1H , CH, J = 12.0 Hz), 4.91 (d, 1H , CH_2 benzyl, J = 15.8 Hz) , 5.11 (d , 1H , CH , J = 12.0 Hz) , 5.36 (d, 1H , CH_2 benzyl, J = 12.0 Hz) , 7.07 - 7.42 (m, 11H ,6,8 H, phenyl protons, benzyl protons) , 7.40 (dd, 1H ,7H, J = 7.1, 1.4 Hz) , 7.50 (dd,1H,9H, J = 14.2 Hz) ; ir (potassium bromide) : 700 (C-S) , 1385 (C-CH_3) , 1670 (C=O ester) , 1740 (C=O amide) cm^{-1} .

Anal . Calcd for C_{26} H_{25} N O_3 S : C , 72. 36 ; H, 5.84 ; N ,3.25; S, 7.43. Found : C, 72.51 ; H , 5.82; N, 3.30 ; S, 7.32 .

5- (3- methyl benzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (10)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 3- methyl benzyl bromide (0,55 g , 3 mmoles) and potassium hydroxide (0,17 g ,3 mmoles) . 0,30 g (30%) was Obtained of 5- (3-methyl benzyl) -4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (10) , mp 104° ; ^{1}H nmr (deuteriochloroform): δ 1.12 (t,3H , CH_3 , J = 7.1 Hz) , 2.31 (S , 3H , CH_3 benzyl) , 4.06 (d , 1H CH, J = 12.3 Hz) , 4.07 (m, 2H, COOCH2), 5.05(d , 1H , CH_2 benzyl, J = 15.4 Hz), 5.08 (d, 1H , CH, J = 12.3 Hz) , 5.15 (d , 1H , CH_2 benzyl , J = 15.4 Hz) , 7.03 - 7.13 (m, 2H ,6,7 H) , 7.06 (S, 1H ,o-benzyl) , 7.17 (t,1H,m-benzyl, J = 7.5 Hz), 7.14 – 7.26 (m, 6 H, 8 H, phenyl protons), 7.38 –

7.43 (m, 2H, o,p-benzyl), 7.48 (dd, 1H, 9 H, J = 7.3 Hz) ; ir (potassium bromide) : 700 (C-S) , 1390 (C-CH_3) , 1670 (C=O ester) , 1750 (C=O amide) cm^{-1} .

Anal . Calcd for C_{26} H_{25} N O_3 S : C , 72. 36 ; H, 5.84 ; N ,3.25; S, 7.43. Found : C, 72.63 ; H , 5.82; N, 3.36 ; S, 7.42 .

5- (4- methyl benzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (11)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 4- methyl benzyl bromide (0,55 g , 3 mmoles) and potassium hydroxide (0,17 g ,3 mmoles) . 0,15 g (15%) was Obtained of 5- (4-methyl benzyl)-4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (11) , mp 170° ; ^{1}H nmr (deuteriochloroform): δ 1.12 (t,3H , CH_3 , J = 7.2 Hz) , 2.30 (S, 3H , CH_3 benzyl) , 4.03 (d , 1H, CH, J = 12.1 Hz) ,4.05 (m, 2H, $COOCH_2$), 5.04 (d , 1H, CH_2 benzyl, J = 15.1 Hz), 5.05 (d, 1H , CH, J = 12.1 Hz), 5.14 (d , 1H , CH_2 benzyl , J = 15.1 Hz) , 7.05 - 7.09 (m, 2H , o- phenyl) , 7.07 (d, 2H ,m-benzyl, J = 8.4 Hz) , 7.18 – 7.26 (m,4H, 6,7,8,9 H), 7.20 (d, 2 H, 0-benzyl, J = 8.4 Hz), 7.40 - 7.43 (m, 3H, o,p-phenyl) ; ir (potassium bromide) : 695 (C-S) , 1385 (C-CH_3) , 1670 (C=O ester) , 1740 (C=O amide) cm^{-1}.

Anal . Calcd for C_{26} H_{25} N O_3 S : C , 72. 36 ; H, 5.84 ; N ,3.25; S, 7.43. Found : C, 71.98 ; H, 5.72; N, 3.23 ; S, 7.10

5- (2- bromobenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (12)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 2- bromo benzyl bromide (0,75 g , 3 mmoles) and potassium hydroxide (0,17 g ,3 mmoles) . 0,3 g (30%) was Obtained of 5- (2-bromo benzyl) -4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (12) , mp 166° ; ^{1}H nmr (deuteriochloroform): δ 1.11(t,3H , CH_3 , J = 7.1 Hz) , 4.05 (m , 2H,$COOCH_2$) ,4.11 (d, 1H, CH, J = 12.0 Hz), 5.07 (d , 1H , CH_2 benzyl, J = 16.6 Hz), 5.09 (d, 1H , CH, J = 12.0 Hz) , 5.41 (d , 1H , CH_2 benzyl , J = 16.6 Hz) , 7.05 - 7.11 (m, 2H ,6, 7 H) , 7.20- 7.28 (m, 7H ,8 H, CH benzyl, o-benzyl, phenyl protons) , 7.32 - 7.43 (m,2H, m,0-benzyl), 7.51 (dd, 1 H, 9 H, J = 7.8, 1.3 Hz), 7.60 (dd, 1H, m-benzyl, J = 7.7, 1.3 Hz) ; ir (potassium bromide) : 660 (C-Br) , 695 (C-S) , 1670 (C=O ester) , 1740 (C=O amide) cm^{-1}.

Anal . Calcd for C_{25} H_{22} BrN O_3 S : C , 60. 43 ; H, 4.46 ; Br, 16.09; N ,2.82; S, 6.45. Found: C, 60.53 ; H , 4.48;Br, 15.87; N, 2.83 ; S, 6.38.

5- (3- bromobenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (13)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 3- bromo benzyl bromide (0,75 g , 3 mmoles) and potassium hydroxide (0,17 g ,3 mmoles) . 0,4 g (40%) was Obtained of 5- (3-bromo benzyl) -4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (13) , mp 104° ; ^{1}H nmr (deuteriochloroform): δ 1.12(t,3H , CH_3 , J = 7.1 Hz) , 4.03 (d, 1H, CH, J = 12.0 Hz), 4.05 (m , 2H,$COOCH_2$) , 5.04 (d , 1H , CH_2 benzyl, J = 15.4 Hz), 5.05 (d, 1H , CH, J = 12.0 Hz) , 5.14 (d , 1H , CH_2 benzyl , J = 15.4 Hz) , 7.02 - 7.06 (m, 2H ,6, 7 H), 7.13 (t, 1H, m-benzyl) , 7.21- 7.26 (m, 6H ,8 H, phenyl protons) , 7.27 (d el, 1H, 0-benzyl, J = 7.7 Hz), 7.37 (dd, 1 H, 9 H, J = 8.4, 1.5 Hz), 7.47 (dd, 1H, p-benzyl, J = 7.7 Hz), 7.49 (s, 1H, 0-benzyl) ; ir (potassium bromide) : 660 (C-Br) , 690 (C-S) , 1670 (C=O ester) , 1740 (C=O amide) cm^{-1}.

Anal. Calcd for C_{25} H_{22} BrN O_3 S: C, 60. 43; H, 4.46; Br, 16.09; N, 2.82; S, 6.45. Found: C, 60. 37; H, 4.44; Br, 16.04; N, 2.91; S, 6.24.

5- (4- bromobenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (14)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 4- bromo benzyl bromide (0,75 g , 3 mmoles) and potassium hydroxide (0,17 g ,3 mmoles) . 0,43 g (43%) was Obtained of 5- (4-bromo benzyl) -4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (14) , mp 155° ; 1H nmr (deuteriochloroform): δ 1.08(t,3H , CH3 , J = 7.1 Hz) , 4.00 (d, 1H, CH, J = 12.0 Hz), 4.02 (m , 2H,$COOCH_2$) , 4.90 (d , 1H , CH_2 benzyl, J = 15.1 Hz), 5.02 (d, 1H , CH, J = 12.0 Hz) , 5.21 (d , 1H , CH_2 benzyl , J = 15.1 Hz) , 6.98 - 7.03 (m, 2H ,6, 7 H), 7.16 (m, 2H, o-benzyl) , 7.19- 7.25 (m, 3H ,8 H, o-phenyl) , 7.32- 7.39 (m, 3H, m,p-phenyl), 7.35 (d, 2 H, m-benzyl), 7.44 (d, 1H, 9 H, J = 7.4 Hz); ir (potassium bromide) : 660 (C-Br) , 695 (C-S) , 1680 (C=O ester) , 1740 (C=O amide) cm^{-1}.

Anal . Calcd for C_{25} H_{22} BrN O_3 S : C , 60. 43 ; H, 4.46 ; Br, 16.09; N ,2.82; S, 6.45. Found: C, 60.64 ; H , 4.48;Br, 16.18; N, 2.83 ; S, 6.01.

5- (3- methoxybenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (15)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 3- methoxybenzyl bromide (0.72 g , 3 mmoles) and potassium hydroxide (0.17 g ,3 mmoles) . 0.58 g (58%) was Obtained of 5- (3-methoxy benzyl) -4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (15) , mp 127° ; ^{1}H nmr (deuteriochloroform): δ 1.11(t,3H , CH3 , J = 7.2 Hz) , 3.76 (s, 3H, OCH_3), 4.05 (d , 1H,CH, J = 12.1 Hz) , 4.06 (m, 2H , COO CH_2), 5.07 (d, 1H , CH, J = 12.1 Hz) , 5.08 (d , 1H , CH_2 benzyl , J = 15.5 Hz), 5.17 (d, 1H , 7 H, J = 15.3 Hz), 6.78 (d, 1H, p-benzyl, J = 8.0 Hz) , 6.87 (d, 1H , o-phenyl, J = 8.0 Hz) , 6.89 (s, 1H , o-phenyl), 7.02 - 7.07 (m, 2 H, 6, 7 H), 7.18 (t, 1H, m-benzyl, J = 8.0 Hz), 7.22 - 7.26 (m, 4H, 8 H, m,p-phenyl), 7.36 - 7.43 (m, 2H, o-phenyl), 7.48 (d el, 1H, 9 H, J = 7.2 Hz); ir (potassium bromide) : 700 (C-S) , 1670 (C=O ester), 1750 (C=O amide), 2840 (OCH_3) cm^{-1}.

Anal. Calcd for C_{26} H_{25} N O_4 S: C, 69. 78; H, 5.63; N, 3.13; S, 7.16. Found : C, 69.47 ; H, 5.54; N, 3.29 ; S, 7.03.

5- (3,5- dimethoxybenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (16)

In the same manner as (6) , was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 3,5- dimethoxybenzyl bromide (0.69 g , 3 mmoles) and potassium hydroxide (0.17 g ,3 mmoles) . 0.35 g (35%) was Obtained of 5- (3,5-dimethoxy benzyl) -4-oxo-2- phenyl -2,3,4,5 – tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (16) , mp 50° ; 1H nmr (deuteriochloroform): δ 1.10(t,3H , CH3 , J = 7.1 Hz) , 3.74 (s, 6H,2OCH_3), 4.05 (d , 1H,CH, J = 12.0 Hz) , 4.08 (m, 2H , COO CH_2), 5.04 (d, 1H , CH_2 benzyl, J = 15.1 Hz) , 5.06 (d , 1H , CH, J = 12.0 Hz) , 5.12 (d, 1H , CH_2 benzyl, J = 15.1 Hz), 6.32 (t, 1H, p-benzyl, J = 2.2 Hz) , 6.48 (d, 2H , o-phenyl, J = 2.2 Hz) , 7.03 - 7.07 (m, 2 H, 6, 7 H), 7.18 – 7.50 (m, 7H, 8 H, phenyl protons); ir (potassium bromide) : 700 (C-S) , 1660 (C=O ester), 1750 (C=O amide), 2840 (OCH_3) cm^{-1}.

Anal. Calcd for C_{27} H_{27}N O_5 S: C, 67. 91; H, 5. 70; N, 2. 93; S, 6. 71. Found: C, 67. 45; H, 5.47; N, 2.91; S, 6.15.

5- (2,6- dichlorobenzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (17)

In the same manner as (6), was prepared from 4-oxo-2- phenyl - 2,3,4,5 - tetra hydro - 1,5- benzothiazepine -3- ethyl carboxylate (3) (1g ,3 mmoles) and 2,6- dichlorobenzyl bromide (0.71 g , 3 mmoles) and potassium hydroxide (0.17 g ,3 mmoles) . 0.43 g (43%) was Obtained of 5- (2,6-dichloro benzyl) -4-oxo-2- phenyl -2,3,4,5 - tetra hydro -1,5- benzothiazepine -3- ethyl carboxylate (17) , mp 202° ; 1H nmr (deuteriochloroform): δ 1.09(t,3H , CH3 , J = 7.1 Hz) , 3.91 (d, 1H,CH, J = 12.0 Hz), 4.05 (m , 2H,COOCH2) , 5.01 (d , 1H , CH, J = 12.0 Hz), 5.19 (d, 1H , CH2 benzyl, J = 14.2 Hz) , 5.58 (d , 1H , CH2 benzyl, J = 14.2 Hz) , 6.92- 6.98 (m, 3H, m,p-benzyl) , 7.17- 7.28 (m, 8H , 6, 7, 8 H, phenyl protons) , 7.42 (dd, 1 H, 9 H, J = 7.0, 1.2 Hz) ; ir (potassium bromide) : 680 (C-Cl), 700 (C-S), 1665 (C=O ester), 1745 (C=O amide) cm-1.

Anal. Calcd for C25 H21Cl2N O3 S: C, 61. 73; H, 4.35; Cl, 14. 5; N, 2. 88; S, 6.59. Found: C, 61. 84; H, 4.25; Cl, 14. 26; N, 3.06; S, 6.80.

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