SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS III.† SYNTHESIS OF NEW BICYCLIC β-LACTAM RING SYSTEM, 12-OXO-4,8-DITHIA-1-AZABICYCLO-[8.2.0]DODEC-2-ENES

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Abstract — N-(α-Ethoxycarbonyl-β,β-diethoxyethyl)-3-phenyl-4-styryl-2-azetidinone (2) was converted to 2-ethoxycarbonyl-12-oxo-11-phenyl-4,8-dithia-1-azabicyclo[8.2.0]dodec-2-ene (11) by the following reactions, namely ozonolysis, reduction, tosylation, thioacetalisation and halogenation. Similarly, 2-ethoxycarbonyl-12-oxo-4,8-dithia-1-azabicyclo[8.2.0]dodec-2-ene (12) was synthesised from N-(α-ethoxycarbonyl-β,β-diethoxyethyl)-4-styryl-3-thiophenoxy-2-azetidinone (3).

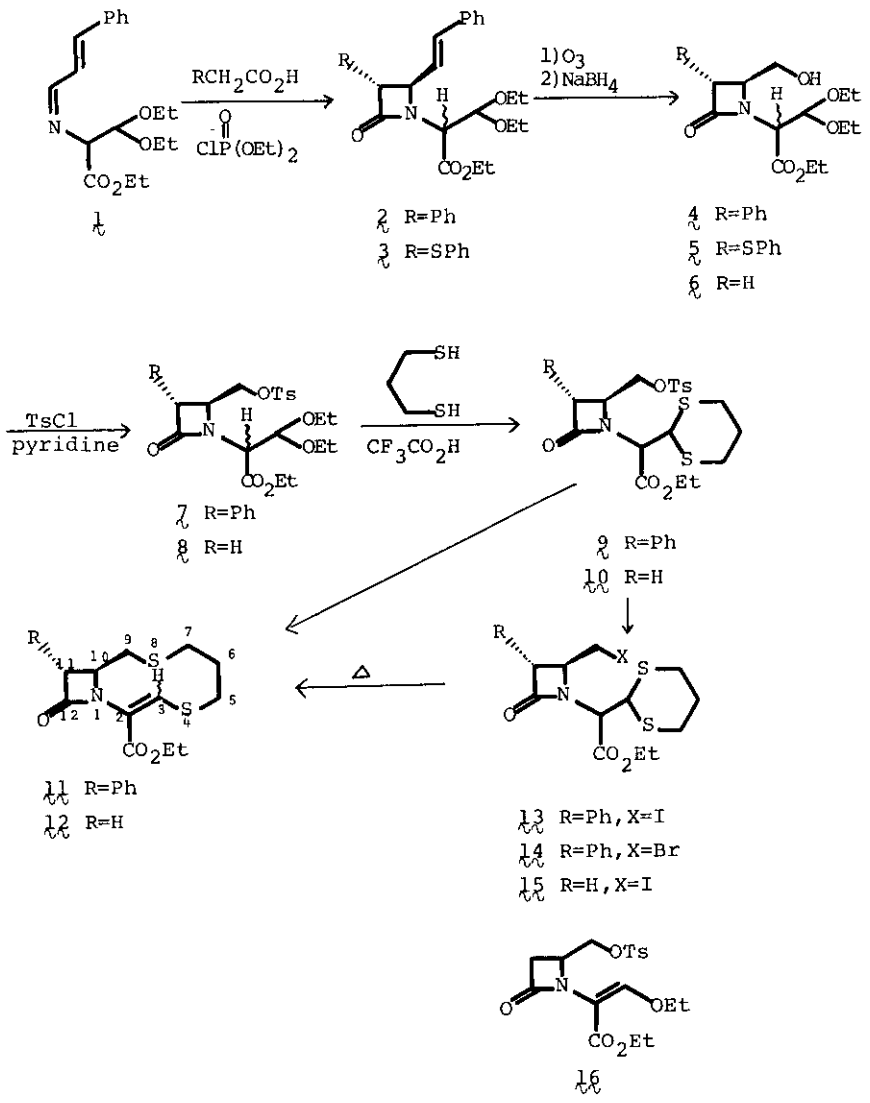
The novel bicyclic β-lactams, clavulanic acid,[1] thienamycin,[2] MM 4550,[3] MM 13902[3] and MM 17880,[4] MC 696-SY2-A,[5] and PS-5[6], have recently been isolated from Streptomyces species. They have characteristic antibiotic activities. In a search for chemotherapeutically useful agents, novel fused bicyclic β-lactams, incorporating the 1-carbadethiacephem,[7] 1-oxadethiapenam,[8,9] and penem[10] ring systems have been synthesised. We here wish to report the facile synthesis of a new bicyclic β-lactam system in the form of 2-ethoxycarbonyl-12-oxo-4,8-dithia-1-azabicyclo[8.2.0]dodec-2-nens (11 and 12).

Condensation of the imine (1),[11] prepared from cinnamaldehyde and ethyl α-amino-β,β-diethoxypropionate, with phenylacetic acid in the presence of diethyl phosphorochloridate[12,13] gave a diastereoisomeric mixture of the 2-azetidinones (2). On recrystallisation from ethanol the two compounds were obtained as pure isomers in 21.9 % and 21.3 % yields. Since the hydrogen at C_3-position of both compounds were seen to have a small coupling constant (J = 2 Hz) in their nmr spectra, the stereo-

chemistry of substituents on the azethidinone ring should be trans.[12] Ozonolysis of the above mixture (2) in methylene chloride at -78°C, followed by reduction with sodium borohydride, yielded a mixture of the alcohols (4) in 56 % yield. Treatment of 4 with p-toluenesulphonyl chloride in pyridine at room temperature afforded a mixture of the tosylates (7) in 90.9 % yield. Stirring the tosylates (7) and 1,3-propanedithiol in trifluoroacetic acid for 3 h at room temperature, followed by purification using silica gel column chromatography, gave the thioacetal (9) as crystals, mp 108 ∿ 110°C. From this reaction the novel bicyclic compound (11) was also obtained in very poor yield (2.97 %). The structure of 11, mp 161 ∿ 162°C, was assigned by spectroscopic analysis, m/e 363 (M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 and 1710 (C=O), δ (CCl_4) 7.52 (1H, s, C_3-H). The compound (11) was more effectively synthesised by heating the halides (13 and 14) derived from the thioacetal (9). Namely, 9 was converted to the iodide (13) (52.4 %), or the bromide (14) (54.2 %), by refluxing with sodium iodide or sodium bromide in acetone. Heating the iodide (13) in ethanol for 72 h gave 11 in 81 % yield. During the halogenation in hot ethanol, 11 was also formed in about 25 % yield along with the halides.

Compound (12) was similarly synthesised as follows. A stereoisomeric mixture of trans-azetidinones (3), obtained in 40.7 % yield from the imine (1) and thiophenoxyacetic acid, was converted to the alcohols (5) in 45.9 % yield. Refluxing 5 with Raney nickel in ethanol furnished the 3-unsubstituted compounds (6) in 98.9 % yield. After tosylation (83.3 %), reaction of the tosylates (8) with 1,3-propanedithiol in trifluoroacetic acid provided the thioacetals (10) in 59.7 % yield, together with a small amount of the enol ether (16). Treatment of the thioacetal (10) with sodium iodide in acetone at room temperature yielded the iodide (15) in 77.5 % yield, while refluxing 10 in the presence of sodium iodide in the same solvent gave the desired bicyclic compound (12) in moderate yield.

We are investigating antibacterial activities of the new compounds whose preparations have been described in this paper.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ClP(OEt)2
1) O3
2) NaBH4
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2 R=Ph
3 R=SPh
4 R=Ph
5 R=SPh
6 R=H
TsCl
pyridine
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7 R=Ph
8 R=H
9 R=Ph
10 R=H
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11 R=Ph
12 R=H
13 R=Ph, X=I
14 R=Ph, X=Br
15 R=H, X=I
16

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus (MP-S2) and are uncorrected. Ir spectra were measured with a Hitachi 215 spectrometer, nmr spectra with a JNM-PMX-60 spectrometer (tetramethylsilane as internal reference), and mass spectra with Hitachi M-53 and JEOL JMX-D 300 mass spectrometers.

1-(α-Ethoxycarbonyl-β,β-diethoxyethyl)-3-phenyl-4-styryl-2-azetidinone (2)

A solution of 2.89 g of phenylacetic acid and 3.65 g of diethyl phosphorochloridate in 500 ml of methylene chloride was stirred at room temperature under a nitrogen atmosphere for 20 min. To this solution was added dropwise a solution of the imine (1)[11] (prepared from 3.21 g of trans-cinnamaldehyde and 5 g of ethyl α-amino-β,β-diethoxypropionate) and 4.29 g of triethylamine in 200 ml of methylene chloride over a period of 1 h, and stirring was continued overnight. The reaction mixture was then washed with water and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue which was purified by column chromatography on 400 g of silica gel, using n-hexane-ethyl acetate (10 : 1 v/v) as eluent, to give a diasteroisomeric mixture of 2-azetidinone (2). Recrystallisation of this product from ethanol gave 1.95 g (21.9 %) of one component as colourless plates, mp 96 ∿ 97°C, ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1740 (C=O); nmr (CCl_4) δ : 1.14 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 1.20 (6H, t, J = 7 Hz, 2 x $OCH_2\underline{CH_3}$), 3.35 ∿ 3.83 (4H, m, 2 x $OC\underline{H_2}CH_3$), 4.10 (1H, d, J = 2 Hz, C_3-H), 4.15 (2H, q, J = 7 Hz, $OC\underline{H_2}CH_3$), 4.28 ∿ 4.50 (1H, m, C_4-H), 4.65 (1H, d, J = 5 Hz, $>C<^{\underline{H}}_{CO_2Et}$), 5.00 (1H, d, J = 5 Hz, >CH), 6.16 ∿ 6.78 (2H, m, $\underline{H}>=<^{H}_{Ph}$), 7.05 ∿ 7.70 (10H, m, 10 x ArH); ms m/e : 437 (M^+). Anal. Calcd. for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.20; H, 7.33; N, 3.18.

Recrystallisation of the solid which was obtained by evaporation of the mother liquid gave 1.9 g (21.3 %) of the second product as colourless plates, mp 77 ∿ 79°C, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1750, 1740 (C=O); nmr (CCl_4) δ : 0.96 ∿ 1.23 (9H, m, 3 x $OCH_2\underline{CH_3}$), 3.30 ∿ 3.83 (4H, m, 2 x $OC\underline{H_2}CH_3$), 4.06 (1H, d, J = 2 Hz, C_3-H), 4.18 (2H, q, J = 7 Hz, $OC\underline{H_2}CH_3$), 4.34 (1H, d, J = 7 Hz, $>C<^{\underline{H}}_{CO_2Et}$), 4.86 (1H, d, J = 7 Hz, >CH), 6.10 ∿ 6.83 (2H, m, $\underline{H}>=<^{H}_{Ph}$), 7.10 ∿ 7.50 (10H, m, 10 x ArH); ms m/e : 437 (M^+). Anal. Calcd. for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.25; H, 7.12; N, 3.28.

1-(α-Ethoxycarbonyl-β,β-diethoxyethyl)-4-hydroxymethyl-3-phenyl-2-azetidinone (4)

A solution of 444 mg of the stereoisomeric mixture of 2 in 200 ml of dry methylene

chloride was ozonised at -78°C until the solution turned bluish-green, whereupon the ozone was replaced by a stream of dry nitrogen. When the excess ozone had been purged, 1 ml of dimethyl sulphide was added and the solution was allowed to stand at room temperature for 1 h. The solution was washed with water and with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue which was purified by column chromatography on 15 g of silica gel, using ether as eluent, to give 280 mg (76 %) of an oil, whose nmr spectrum showed the proton due to aldehyde. This product was used in the next step without further purification. A solution of 280 mg of the crude aldehyde in 15 ml of ethanol and 5 ml of water was cooled to 0 ∿ 5°C in an ice bath, 20 mg of sodium borohydride added and the resulting solution stirred for 30 min at 0 ∿ 5°C. The solution was then brought ot pH 4 by addition of 10 % hydrochloric acid. Evaporation of the solvent gave an oily residue to which was added 20 ml of water, and the resulting solution was extracted with methylene chloride. The extract was dried over Na_2SO_4, and evaporated to give the crude alcohol which was purified by column chromatography on 9 g of silica gel, using n-hexane-ethyl acetate (5 : 1 v/v) as eluent, to give 205 mg (72.7 %) of the alcohol (4) as a yellow oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 3500 (OH), 1750, 1740 (C=O); nmr (CCl_4) δ : 1.00 ∿ 1.53 (9H, m, 3 x $OCH_2\underline{CH_3}$), 7.25 (5H, s, 5 x ArH).

1-(α-Ethoxycarbonyl-β,β-diethoxyethyl)-3-phenyl-4-tosyloxymethyl-2-azetidinone (7)

A mixture of 133 mg of the alcohols (4), 104 mg of p-toluenesulphonyl chloride and 0.4 ml of pyridine was stirred for 15 h at room temperature. To this mixture was added 30 ml of benzene and the solution was washed with saturated potassium bisulphate solution and with water, dried over Na_2SO_4, and evaporated to give the crude product. Purification by column chromatography on 8 g of silica gel, using ether as eluent, gave 170 mg (90.9 %) of the tosylates (7) as a yellow oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1750, 1740 (C=O), 1350 (SO_2); nmr (CCl_4) δ : 0.93 ∿ 1.45 (9H, m, 3 x $OCH_2\underline{CH_3}$), 2.40 (3H, s, $ArCH_3$), 3.30 ∿ 3.83 (4H, m, 2 x $OCH_2\underline{CH_3}$), 7.20 (2H, d, J = 8 Hz, 2 x ArH), 7.23 (5H, s, 5 x ArH), 7.70 (2H, d, J = 8 Hz, 2 x ArH).

1-(α-Ethoxycarbonyl-β,β-trimethylenedithioethyl)-3-phenyl-4-tosyloxymethyl-2-azetidinone (9)

A mixture of 960 mg of the tosylates (7), 900 mg of 1,3-propanedithiol and 3 ml of trifluoroacetic acid was stirred for 3 h at room temperature. After addition of 100 ml of chloroform, the solution was washed with 0.25 N sodium hydroxide solution

and with water, dried over Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography on 40 g of silica gel, using n-hexane-ethyl acetate (5 : 1 v/v) as eluent, to give 560 mg (53 %) of the thioacetal (9) as a yellow oil. Recrystallisation from ethanol afforded colourless crystals, mp 108 ∿ 110°C, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1760, 1740 (C=O); nmr (CCl_4) δ : 1.27 (3H, t, J = 7 Hz, $OCH_3\underline{CH_3}$), 1.83 ∿ 2.25 (2H, m, $SCH_2\underline{CH_2}CH_2S$), 2.48 (3H, s, $ArCH_3$), 4.16 (1H, d, J = 10 Hz, $\rangle C\langle^{\underline{H}}_{CO_2Et}$), 4.22 (2H, q, J = 7 Hz, $O\underline{CH_2}CH_3$), 4.97 (1H, d, J = 10 Hz, ⟩CH), 7.30 (5H, s, 5 x ArH), 7.42 (2H, d, J = 8 Hz, 2 x ArH), 7.82 (2H, d, J = 8 Hz, 2 x ArH). Anal. Calcd. for $C_{25}H_{29}NO_6S_3 \cdot H_2O$: C, 54.25; H, 5.28; N, 2.53. Found : C, 53.96; H, 5.32; N, 2.62.

1-(α-Ethoxycarbonyl-β,β-trimethylenedithioethyl)-4-iodomethyl-3-phenyl-2-azetidinone (13)

A mixture of 380 mg of the thioacetal (9) and 1.06 g of sodium iodide in 30 ml of acetone was refluxed for 48 h. Evaporation of the solvent gave an oily residue to which was added 50 ml of ether. The resulting mixture was washed with 10 % sodium thiosulphate and with water, dried over Na_2SO_4 and evaporated. The oily residue was purified by column chromatography on 15 g of silica gel, using n-hexane-ethyl acetate (20 : 1 v/v) as eluent, to give 183 mg (52.4 %) of the iodide (13) as a yellow oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1760, 1740 (C=O); nmr (CCl_4) δ : 1.34 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 1.80 ∿ 2.33 (2H, m, $SCH_2\underline{CH_2}CH_2S$), 4.25 (1H, d, J = 10 Hz, $\rangle C\langle^{\underline{H}}_{CO_2Et}$), 4.28 (2H, q, J = 7 Hz, $O\underline{CH_2}CH_3$), 5.18 (1H, d, J = 10 Hz, ⟩CH), 7.20 ∿ 7.73 (5H, m, 5 x ArH).

1-(α-Ethoxycarbonyl-β,β-trimethylenedithioethyl)-4-bromomethyl-3-phenyl-2-azetidinone (14)

A mixture of 600 mg of the thioacetal (9) and 1.5 g of sodium bromide in 60 ml of acetone was refluxed for 24 h. Evaporation of the solvent gave an oily residue to which was added 100 ml of ether. The mixture was washed with 10 % sodium thiosulphate solution and with water, dried over Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography on 30 g of silica gel, using n-hexane-ethyl acetate (5 : 1 v/v) as eluent, to give 270 mg (54.2 %) of the bromide (14) as a yellow oil. Recrystallisation from ethanol afforded colourless plates, mp 96 ∿ 98°C, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1760, 1740 (C=O); nmr (CCl_4) δ : 1.27 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 1.83 ∿ 2.30 (2H, m, $SCH_2\underline{CH_2}CH_2S$), 2.40 ∿ 3.24 (4H, m, $S\underline{CH_2}CH_2\underline{CH_2}S$),

4.15 (1H, d, J = 10 Hz, $>C<^{H}_{CO_2Et}$), 4.27 (2H, q, 7 Hz, $OC\underline{H}_2CH_3$), 5.15 (1H, d, J = 10 Hz, $>CH$), 7.23 ∿ 7.63 (5H, m, 5 x ArH), ms m/e : 443 (M^+). Anal. Calcd. for $C_{18}H_{22}NO_3S_2Br$: C, 48.66; H, 4.99; N, 3.15. Found : C, 48.95; H, 5.04; N, 3.30.

2-Ethoxycarbonyl-12-oxo-11-phenyl-4,8-dithio-1-azabicyclo[8.2.0]dodec-2-ene (11)

A solution of 35 mg of the iodide (13) in 20 ml of ethanol was refluxed for 72 h. Evaporation of the solvent gave an oily residue, which was purified by column chromatography on 1 g of silica gel, using n-hexane-ethyl acetate (10 : 1 v/v) as eluent, to give 21 mg (81 %) of 11 as a yellow oil, which was crystallised from ethanol as colourless plates, mp 161 ∿ 162°C, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1760, 1710 (C=O); nmr (CCl_4) δ : 1.27 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$), 4.48 (1H, d, J = 2 Hz, C_{11}-H), 4.76 ∿ 4.96 (1H, m, C_{10}-H), 7.15 ∿ 7.50 (5H, m, 5 x ArH), 7.52 (1H, s, C_3-H), ms m/e : 363 (M^+). Anal. Calcd. for $C_{18}H_{21}NO_3S_2$: C, 59.49; H, 5.83; N, 3.86. Found : C, 59.06; H, 6.08; N, 3.88.

1-(α-Ethoxycarbonyl-β,β-diethoxyethyl)-4-styryl-3-thiophenoxy-2-azetidinone (3)

A solution of 8.25 g of thiophenoxyacetic acid and 8.52 g of diethyl phosphorochloridate in 1000 ml of dry methylene chloride was stirred at room temperature for 40 min under nitrogen. To this solution was added dropwise a solution of the imine (1)[11] (prepared from 6.48 g of cinnamaldehyde and 10.06 g of amine) and 9.92 g of triethylamine in 600 ml of dry methylene chloride over a period of 1 h, and stirring was continued overnight. The reaction mixture was worked up as described above for 2, affording 9.38 g (40.7 %) of 3 as a pale yellow oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1765, 1735 (C=O); nmr ($CDCl_3$) δ : 1.08 (6H, t, J = 7 Hz, 2 x $OCH_2C\underline{H}_3$), 1.22 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$), 3.27 ∿ 3.83 (4H, m, 2 x $OC\underline{H}_2CH_3$), 4.07 (1H, d, J = 2.2 Hz, C_3-H), 4.10 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 4.25 (1H, dd, J = 8 Hz, J = 2.2 Hz, C_4-H), 4.33 (1H, d, J = 8 Hz, $>NC\underline{H}CO_2Et$), 4.76 [1H, d, J = 8 Hz, $-C\underline{H}(OEt)_2$], 6.22 (1H, dd, J = 16 Hz, J = 8 Hz, $\underline{H}>=<^{H}_{Ar}$), 6.72 (1H, d, J = 16 Hz, $H>=<^{H}_{Ar}$), 7.13 ∿ 7.70 (10H, m, 10 x ArH); ms m/e : 469 (M^+).

1-(α-Ethoxycarbonyl-β,β-diethoxyethyl)-4-hydroxymethyl-3-thiophenoxy-2-azetidinone (5)

A solution of 4.28 g of 3 in 200 ml of dry methylene chloride was ozonized at -78°C, until the solution turned bluish-green, whereupon the ozone was replaced by a stream of nitrogen. When the excess ozone had been purged, 5 ml of dimethyl sulphide was

added. Workup as already described for the analagous compound gave 3.16 g of the crude aldehyde as a brown oil. The crude aldehyde was dissolved in 70 ml of 99 % ethanol and 152 mg of sodium borohydride added to the solution at -10°C. The solution was stirred for 1 h at room temperature and worked up as described above for 4 to give 1.97 g (45.9 %) of 5 as a pale yellow oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 3500 (OH), 1760, 1740 (C=O); nmr ($CDCl_3$) δ : 1.03 ∿ 1.50 (9H, m, 3 x $OCH_2\underline{CH}_3$), 3.37 ∿ 5.07 (13H, m, OH, 4 x CH and 4 x CH_2), 7.40 ∿ 7.90 (5H, m, 5 x ArH); ms m/e : 397 (M^+); m/e Calcd. for $C_{19}H_{27}NO_6S$: 397.1559 (M^+). Found : 397.1600 (M^+).

1-(α-Ethoxycarbonyl-β,β-diethoxyethyl)-4-hydroxymethyl-2-azetidinone (6)

A solution of 1.33 g of 5 in 50 ml of 99 % ethanol was refluxed for 10 min with a large excess of Raney nickel. The reaction mixture was filtered and the ethanol removed by evaporation. The oily residue was dissolved in chloroform and the solution was washed with brine, dried over Na_2SO_4, and evaporated to yield 961 mg (98.8 %) of 6 as a colourless oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 3500 (OH), 1750 (C=O); nmr ($CDCl_3$) δ : 1.00 ∿ 1.50 (9H, m, 3 x $OCH_2\underline{CH}_3$), 3.03 (2H, d, J = 4 Hz, $C\underline{H}_2OTs$), 3.02 ∿ 4.47 (11H, m, 3 x CH and 4 x CH_2), 4.67 ∿ 5.00 (2H, m, 2 x CH); ms m/e : 289 (M^+).

1-(α-Ethoxycarbonyl-β,β-diethoxyethyl)-4-tosyloxymethyl-2-azetidinone (8)

A solution of 3.25 g of 6 and 4.40 g of p-toluenesulphonyl chloride in 6 ml of pyridine was stirred at room temperature for 3 h. The reaction mixture was diluted with chloroform and the organic solution was washed with 10 % hydrochloric acid and with brine, dried over Na_2SO_4, and evaporated to yield 5.38 g of a pale yellow oil. Purification by chromatography on silica gel (16.1 g), using n-hexane-ethyl acetate (5 : 1 v/v) as eluent, gave 4.15 g (83.3 %) of 8 as a colourless oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1755,1740 (C=O); nmr ($CDCl_3$) δ : 0.95 ∿ 1.40 (9H, m, 3 x $OCH_2\underline{CH}_3$), 2.42 (3H, s, $ArCH_3$), 1.68 (1H, dd, J = 16 Hz, J = 2 Hz, C_3-H), 2.90 ∿ 3.37 (1H, m, C_3-H), 3.40 ∿ 4.57 (7H, m, CH and 3 x CH_2), 4.15 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 4.57 (1H, d, J = 4.2 Hz, >CH), 4.85 (1H, d, J = 4.2 Hz, >CH), 7.33 (2H, d, J = 8 Hz, 2 x ArH), 7.78 (2H, d, J = 8 Hz, 2 x ArH); ms m/e : 396 (M^+ - EtOH). Anal.Calcd. for $C_{20}H_{29}NO_8S$: C, 54.17; H, 6.59; N, 3.16. Found : C, 54.54; H, 6.48; N, 2.89.

1-(α-Ethoxycarbonyl-β,β-trimethylenedithioethyl)-4-tosyloxymethyl-2-azetidinone (10) and 1-(α-Ethoxycarbonyl-β-ethoxyvinyl)-4-tosyloxymethyl-2-azetidinone (16)

To a solution of 718 mg of 8 and 1.75 g of 1,3-propanedithiol in 8 ml of dry benzene was added 1.6 ml of trifluoroacetic acid. The mixture was stirred at room temperature for 32 h under nitrogen. The reaction mixture was diluted with benzene, washed with 0.25 N sodium hydroxide and with brine, and dried over Na_2SO_4. The benzene was evaporated to yield 850 mg of a pale yellow oil which was chromatographed on silica gel (42 g), using benzene-acetone (100 : 1 v/v) as eluent, to give 334 mg (59.7 %) of 10. Recrystallisation from 99 % ethanol afforded colourless needles, mp 124.5 ∿ 126°C, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1760 (C=O), 1740 (C=O); nmr ($CDCl_3$) δ : 1.18 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 1.80 ∿ 2.20 (2H, m, CH_2), 2.38 (3H, s, $ArCH_3$), 2.55 ∿ 3.33 (6H, m, 3 x CH_2), 3.93 ∿ 4.50 (6H, m, 2 x CH and 2 x CH_2), 4.88 (1H, d, J = 10 Hz, >CH), 7.33 (2H, d, J = 8 Hz, 2 x ArH), 7.76 (2H, d, J = 8 Hz, 2 x ArH); ms m/e: 459 (M^+). Anal. Calcd. for $C_{19}H_{25}NO_6S_3$: C, 49.67; H, 5.49; N, 3.09. Found: C, 49.19; H, 5.54; N, 2.66. Elution with benzene-acetone (50 : 1 v/v) gave 82 mg of 16 as a colourless oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1760 (C=O), 1710 (C=O), 1645 (C=C); nmr ($CDCl_3$) δ : 1.25 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 1.33 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 2.37 (3H, s, $ArCH_3$), 2.68 (1H, dd, J = 15 Hz, J = 2 Hz, C_3-H), 1.12 (1H, ddd, J = 15 Hz, J = 3 Hz, J = 2 Hz, C_3-H), 3.97 ∿ 4.30 (7H, m, CH and 3 x CH_2), 7.42 (2H, d, J = 8 Hz, 2 x ArH), 7.33 (1H, s, $-C\underline{H}=C\langle_{CO_2Et}$), 7.83 (2H, d, J = 8 Hz, J = 8 Hz, 2 x ArH); ms m/e : 397 (M^+). Anal. Calcd. for $C_{18}H_{23}NO_7S$: C, 54.40; H, 5.83; N, 3.53. Found : C, 54.22; H, 5.71; N, 3.77.

1-(α-Ethoxycarbonyl-β,β-trimethylenedithioethyl)-4-iodomethyl-2-azetidinone (15)

A solution of 285 mg of 10 and 2.79 g of sodium iodide in 40 ml of acetone was stirred at room temperature for 70 h. After evaporation of the acetone at room temperature, the residue was partitioned between water and methylene chloride. The methylene chloride layer was washed with 5 % sodium thiosulphate and with water, and dried over Na_2SO_4. The solvent was evaporated to yield 522 mg of a colourless oil, which was purified by S-X3 gel chromatography, using benzene as eluent, to give 200 mg (77.5 %) of 14 as a colourless oil, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1750 (C=O); nmr ($CDCl_3$) δ : 1.32 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 1.80 ∿ 2.30 (2H, m, CH_2), 2.30 ∿ 4.10 (9H, m, CH and 4 x CH_2), 4.32 (1H, d, J = 10 Hz, $>NC\underline{H}CO_2Et$), 4.33 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 5.12 (1H, d, J = 10 Hz, >CH); ms m/e : 415 (M^+).

2-Ethoxycarbonyl-12-oxo-4,8-dithia-1-azabicyclo[8.2.0]dodec-2-ene (12)

A solution of 20 mg of 10 and 27 mg of sodium iodide in 5 ml of acetone was refluxed

for 26 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate. The extract was washed with 5 % sodium thiosulphate and with water, dried over Na_2SO_4, and evaporated to yield 16 mg of a colourless oil, which was purified by preparative tlc to yield 9 mg of 12 as a colourless syrup, ir $\nu_{max}^{CHCl_3}$ cm^{-1} : 1775 (C=O), 1705 (C=O); nmr ($CDCl_3$) δ : 1.35 (3H, t, J = 7 Hz, $OCH_2\underline{CH}_3$), 1.53 ∿ 2.93 (8H, n, 4 x CH_2), 3.07 (2H, d, J = 4 Hz, C_9-H_2), 4.25 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$), 4.72 ∿ 5.00 (1H, m, C_{10}-H), 7.48 (1H, s, C_3-H), ms m/e : 287 (M^+); m/e Calcd. for $C_{12}H_{17}NO_3S_2$: 287.0648 (M^+). Found : 287.0633 (M^+).

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