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A CONVENIENT SYNTHESIS OF BRIDGED AZATRICYCLIC ANHYDRIDES

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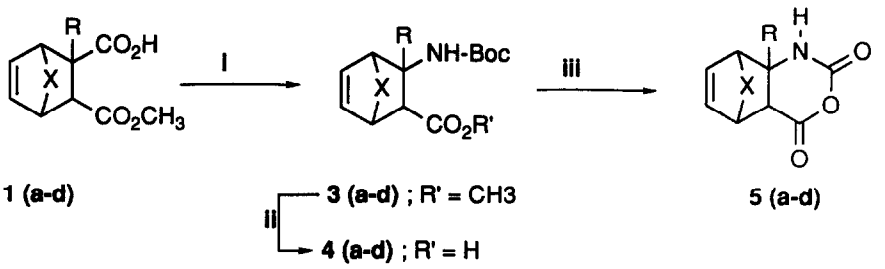
Abstract: *Bridged N-protected β-amino acids have been regioselectively prepared from the corresponding bicyclic monoesters. The subsequent cyclisation by thionyl chloride produced the desired bridged azatricyclic anhydrides which are versatile substrates for the synthesis of dipeptides; they are also converted into oxathymine and oxauracil by a thermal [4+2] cycloreversion.*

In our previous work, we have demonstrated the utility of functionalized bicyclo[2.2.1] heptane derivatives in the synthesis of γ-lactones and (5H)-furanones.[1-4] More recently, these bridged bicyclic systems have attracted a great deal of attention as starting material in the synthesis of natural products[5] and pharmacological agents.[6] Moreover, in the previous studies we have demonstrated the reactivity of isatoic anhydride derivatives with Grignard reagents in the preparation of five- and six- membered 4-(o-aminophenyl)cycloalkanols and their conversion into brofoxine derivatives.[7,8]

In continuation of our research in the field of azaheterocyclic anhydrides, we are now particularly interested in studying the chemistry of bridged azatricyclic anhydrides. Here we report a convenient and general method for the synthesis of bicyclic β-amino acid derivatives and their conversion into the title compounds. The great advantage of our method is that the furan adduct is easily obtained under much milder experimental conditions, in comparison with the previous methods.[9-11]

There are many methods in the literature for the preparation of isatoic anhydrides and saturated derivatives.[12,13] However, their bridged bicyclic analogues have not been described. We took advantage of the Curtus rearrangement to convert the bridged bicyclic monoesters[14] adducts of furan and cyclopentadiene to the corresponding N-Boc protected β-amino acids (Scheme 1).

In order to prepare the bridged bicyclic β-amino acids **4a-4d**, the starting monoesters **1a-1d** were activated with ethyl chloroformate and Et_3N in dry tetrahydrofuran, followed by addition of aqueous sodium azide, to afford the acyl azide. After aqueous work up and extraction with ethyl acetate, the crude acyl azide was dissolved in benzene (in the case of the cyclopentadiene adducts) or methylene chloride (in the case of the furan adducts) and the solution was brought to reflux for 2 h. The addition of *tert*-butyl alcohol in the presence of a catalytic amount of p-toluenesulfonic acid afforded



a : X = CH_2 ,*exo* , R = H **b** : X = CH_2,*endo* , R = H

c : X = CH_2,*endo* , R = CH_3 **d** : X = O,*exo* , R = H

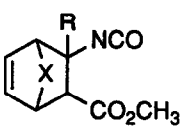
I; (1) $ClCO_2Et$, Et_3N, (2) NaN_3, (3)C_6H_6 or CH_2Cl_2,reflux, (4) t-BuOH,p-TsOH

II; $NaOH/H_2O$-MeOH ; III; $SOCl_2/CH_2Cl_2$

Scheme 1

the N-Boc protected β-amino ester **3a-3d**. Monoesters were thus converted into compounds **3a-3d**, without the need to purify any of the intermediates such as **2a-2d**,in 75-85% overall yields.

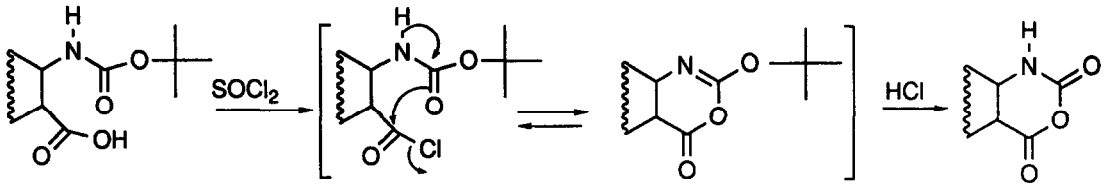
Furthermore, the intermediate isocyanates **2a-2d** could also be treated with $TsOH-H_2O$ to afford the primary amine, a key intermediate in the synthesis of a potent norbonyl derived thromboxane TxA_2 receptor antagonist.[15] The bridged bicyclic β-amino esters **3a-3d**, obtained from isocyanate intermediates **2a-2d**, were converted to the corresponding β-amino acids by a careful saponification with NaOH, in quantitative yield.



2 (a-d)

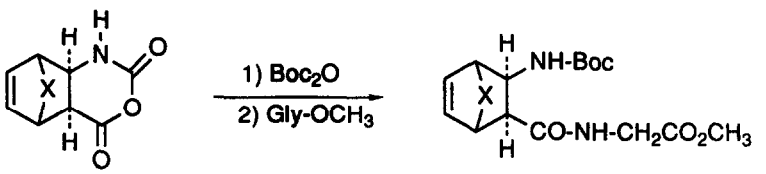
The N-Boc protected bridged bicyclic β-amino acids **4a-4d**, thus obtained, were easily cyclized into bridged azatricyclic anhydrides by a one-pot, two-step sequence as follows. Acyl chloride formation occurred in THF with thionyl chloride, in addition to intramolecular cyclization with liberation of hydrogen chloride and cleavage of the tertio butyl group (Scheme 2). The excess of thionyl chloride and THF were evaporated and the resulting solid was washed with

carbon tetrachloride to afford bridged azatricyclic anhydrides **5a-5d** in high yields, irrespective of the structure of the starting β-amino acids.



Scheme 2

The bridged azatricyclic anhydrides are interesting intermediates because of their general regioselectivity toward nucleophiles. Thus the two *exo* anhydrides **5a** and **5d**, respective adducts of cyclopentadiene and furan, were coupled with the di-*tert*-butyl dicarbonate (Boc_2O) in tetrahydrofuran and triethylamine at room temperature, followed by the addition of glycine methyl ester to afford the corresponding dipeptides **6a** and **6b** in good yields (Scheme 3).

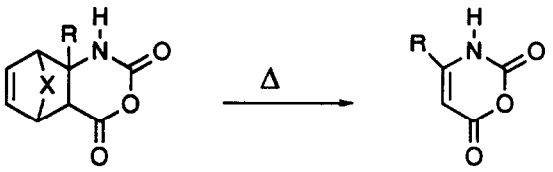


5 a : X = CH2 **6 a**

5 d : X = O **6 b**

Scheme 3

Moreover, for the synthesis of oxathymine **7a** and oxauracil **7b**, the bridged azatricyclic anhydride **5c** and **5d**, were submitted to the retrodiene reaction. According to the method previously reported[2,16] they were heated at their specific melting points. Thus the known compounds[17,18] **7a** and **7b** were easily obtained, respectively in 72% and 85% yields, (Scheme 4).



5c : X = CH_2 ; R = CH_3 **7a** : R = CH_3

5d : X = O ; R = H **7b** : R = H

Scheme 4

In summary, a convenient synthesis of bridged bicyclic β-amino acids and their conversion into bridged azatricyclic anhydrides has been demonstrated. This approach could be applied to a variety of useful intermediates for the synthesis of thromboxane A_2(TxA_2) and its biosynthetic precursor PGH_2 products, based on the use of well known optically active oxabicyclo[2.2.1] heptane monoesters.[19,20]

EXPERIMENTAL

Melting points were determined using an Electrothermal apparatus and are uncorrected. The IR spectra were determined using a Shimatzu IR-435 spectrophotometer. The NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with a Varian EM 360 or Varian XL-200 spectrometer. Mass spectra were obtained on a JEOL D100 spectrometer and HRMS were carried out by the mass spectroscopy Regional center of University of Montreal. Elemental analyses were carried out by the analyses centre of University of Montpellier (France). Column chromatography was performed on silica gel (Kieselgel 60G, E. Merck) and preparative thin-layer chromatography was carried out on 0.25 mm silica gel 60F-254 plates (BDH) or on Kiesegel 60F 254 plates (E. Merck). Petroleum ether and ethyl acetate were distilled before use in chromatography. Tetrahydrofuran and benzene were distilled from sodium, methylene chloride was distilled from calcium hydride immediately prior to use, and triethylamine was distilled from calcium hydride and stored over 3 Å molecular seives. All reactions were performed in oven-dried glassware.

General Procedure: Preparation of N-Boc bridged bicyclic β-amino esters 3a-3d.

Ethyl chloroformate (1.63 g, 15 mmol) was added to a mixture of the monoester **1** (10 mmol) and Et_3N (2.70 ml, 20 mmol) in dry tetrahydrofuran (15 ml) at –20°C. An aqueous solution of NaN_3 (1.62 g, 25 mmol) was added at –10°C. The temperature was gradually raised to room temperature, and stirring was continued for 1 h. The reaction mixture was diluted with H_2O and the product was extracted with ethyl acetate. The organic phase was washed (water, brine), dried (Na_2SO_4), filtered and concentrated to leave the crude acyl azide. The crude acyl azide was dissolved in anhydrous benzene for cyclopentadiene adducts or in dry methylene chloride for furan adducts, and heated under reflux for 2 h. Then t-butanol (10 ml) and a catalytic amount of p-toluenesulfonic acid were added to the resulting solution of isocyanate in benzene or methylene chloride. The mixture was cooled to ambient temperature, and diluted with benzene or methylene chloride. The mixture was washed (water, brine), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography.

The following substances were prepared via this general procedure.

Methyl 3-*exo*-N-*tert*-butoxycarbonylaminobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (3a): 2.34 g (86%) from 2 g (10 mmol) of **1a**; mp 110-112°C (ether-petroleum ether); IR (KBr) 3360, 1730, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H, CH_3), 1.50 (m, 1H, H-7), 1.95 (m, 1H, H-7), 2.50 (dd, 1H, J = 8, 1.5 Hz, H-2), 2.65 (m, 1H, H-1), 2.90 (m, 1H, H-4), 3.65 (s, 3H, CH_3), 3.80 (m, 1H, H-3), 5.10 (br, 1H, NH), 6.20 (m, 2H, H-5, H-6); MS (m/z) 267 (M^+, 2%), 202 (100%); Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.89; H, 7.91; N, 5.23. Found: C, 62.58; H, 7.60; N, 5.01.

Methyl 3-*endo*-N-*tert*-butyloxycarbonylaminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate (3b): 2.2 g (81%) from 2 g (10 mmol) of **1b**; mp 54-55°C (ether-petroleum ether); IR (KBr) 3330, 1740, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H, CH_3), 1.45 (m, 2H, H-7), 3.00 (m, 2H, H-1, H-4), 3.12 (dd, 1H, J = 2, 8Hz, H-2), 3.57 (s, 3H, CH_3), 4.50 (td, 1H, J = 2, 8Hz, H-4), 4.75 (m, 1H, NH), 6.10 (dd, 1H, J = 2.5, 6Hz, H-5), 6.35 (dd, 1H, J = 2.5, 6Hz, H-6); HRMS, calcd for $C_{14}H_{21}NO_4$ (M^+) 267.1471, found 267.1453.

Methyl 3-*exo*-methyl 3-*endo*-N-*tert*-butyloxycarbonylaminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate (3c): 2 g (72%) from 2.1 g of **1c**; mp 111-112°C (ether-petroleum ether); IR (KBr) 3400, 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H, CH_3), 1.48 (m, 2H, H-7), 1.65 (s, 3H, CH_3), 2.71 (d, 1H, J = 2Hz, H-2), 3.06 (m, 1H, H-1), 3.33 (m, 1H, H-4), 3.65 (s, 3H, CH_3), 5.75 (br, 1H, NH), 6.15 (m, 2H, H-5, H-6); HRMS, calcd for $C_{15}H_{23}NO_4$ (M^+) 281.1628, found 281.1654.

Methyl 3-*exo*-N-*tert*-butyloxycarbonylamino-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylate (3d): 2.3 (84%) from 2 g (10 mmol) of **1d**; mp 126-128°C (ethyl acetate-petroleum ether); IR (KBr) 3360, 1720, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H, CH_3), 2.78 (d, 1H, J = 8Hz, H-2), 3.65 (s, 3H, CH_3), 4.20 (dd, 1H, J = 8, 10 Hz, H-3), 4.70 (s, 1H, H-4), 5.10 (s, 1H, H-1), 5.25 (br, 1H, NH), 6.40 (s, 2H, H-5, H-6); MS (m/z) 269 (M^+, 7%), 201 (30%), 201 (100%); Anal. calcd for $C_{13}H_{19}NO_5$: C, 57.79; H, 7.11; N, 5.20. Found: C, 57.59; H, 6.96; N, 5.23.

General Procedure: Preparation of N-Boc bridged bicyclic β-amino acids **4a-4d**.

The β-amino ester **3** (5.5 mmol) was dissolved in methanol (50 ml), and to this solution was added a 2N NaOH solution (15 mmol) at 0°C. The mixture was stirred at room temperature for 2 h. The mixture was acidified with 2N HCl, and extracted with ether. The combined organic extracts were washed (water, brine), dried (Na_2SO_4), and concentrated. The product was crystallized from ether : petroleum ether (1:1).

The following substances were prepared via this general procedure.

3-*exo*-N-*tert*-butyloxycarbonylaminobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (4a): 1.36 g (98%) from 1.5 g (5.5 mmol) of **3a**; mp 116-117°C (ether-petroleum ether); IR (KBr) 3320, 1715, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H, CH_3), 1.60 (m, 1H, H-7), 2.02 (m, 1H, H-7), 2.50 (dd, 1H, J = 1, 8 Hz, H-2), 2.70 (m, 1H, H-1), 2.95 (m, 1H, H-4), 3.95 (m, 1H, H-3), 6.20 (m, 2H, H-5, H-6), 6.50 (br, 1H, NH), 10.30 (br, 1H, OH); MS (m/z) 253 (M^+, 12%), 188 (70%),

132 (100%); Anal. Calc for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.42; H, 7.61; N, 5.91.

3-*endo*-N-*tert*-butyloxycarbonylaminobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (4b): 1.41 g (100%) from 1.5 g (5.5 mmol) of **3b**; mp 126-127°C (ether-petroleum ether); IR (KBr) 3330, 1715, 1710, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H, CH_3), 1.55 (m, 2H, H-7), 3.10 (m, 3H, H-1, H-2, H-4), 6.45 (dd, 2H, J = 2, 6 Hz, H-5, H-6); 6.50 (br, 1H, NH), 10.80 (br, 1H, OH); HRMS, calcd for $C_{13}H_{19}NO_4$ (M^+) 251.1315, found 253.1318.

3-*endo*-N-*tert*-butyloxyamino-3-*exo*-methylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (4c): 1.44 g (98%) from 1.55 g (5.5 mmol) of **3c**; mp 123-124°C (ether-petroleum ether); IR(KBr) 3340, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H, CH_3), 1.51 (m, 2H, H-7), 1.66 (s, 3H, CH_3), 2.76 (d, 1H, J = 2Hz, H-2), 3.13 (m, 1H, H-1), 3.43 (m, 1H, H-4), 6.16 (m, 2H, H-5, H-6), 6.40 (br, 1H, NH), 9.80 (br, 1H, OH); HRMS, calcd for $C_{14}H_{21}NO_4$ (M^+) 267.1471, found 267.1450.

3-*exo*-N-*tert*-butyloxycarbonylamino-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (4d): 1.40 g (100%) from 1.5 g (5.5 mmol) of **3d**; mp 143-145°C (ether-petroleum ether); IR (KBr) 1730, 1700, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H, CH_3), 2.78 (d, 1H, J = 8 Hz, H-2), 4.10 (dd, 1H, J = 8, 10 Hz, H-3), 4.65 (s, 1H, H-4), 5.10 (s, 1H, H-1), 5.60 (br, 1H, NH), 6.50 (s, 2H, H-5, H-6), 11.50 (br, 1H, OH); MS (m/z) 255 (M^+, 3%), 189 (100%); Anal. calcd for $C_{12}H_{17}NO_5$: C, 56.45; H, 6.71; N, 5.48. Found: C, 56.32, H, 6.79; N, 5.88.

General Procedure: Preparation of bridged azatricyclic anhydride **5a-5d**.

To a stirred solution of N-Boc amino acid **3** (4 mmol) in 20 ml of dry THF (nitrogen atmosphere) was added, dropwise, a solution of thionyl chloride (2 ml) in 5 ml of dry THF. The mixture was stirred at room temperature for 2 h. The solvent was removed and the residual solid was washed with carbon tetrachloride (20 ml) to give the azatricyclic anhydride **5**.

The following substances were prepared via this general procedure.

2,7-*exo*-4,6-Oxazatricyclo[6.2.1.$0^{2,7}$]undec-9-ene-3,5-dione (5a): 0.67 g (95%) from 1 g (4 mmol) of **4a**; mp 146-148 °C (carbon tetrachloride); IR (KBr) 3320, 1785, 1720, 1630 cm^{-1}; ^1H NMR (DMSO- d_6) δ 1.36 (q, 2H, J = 9 Hz, H-11), 2.70 (d, 1H, J = 6.5 Hz, H-2), 2.82 (s, 1H, H-8), 3.12 (s, 1H, H-1), 3.26 (d, 1H, J = 6.5 Hz, H-7), 6.13 (d, 1H J = 2.5 Hz, H-9), 6.30 (d, 1H, J = 2.5 Hz, H-10), 8.50 (br, 1H, NH); MS (m/z) 179 (M^+, 3%), 114 (100%); Anal. calcd for $C_9H_9NO_3$: C, 60.32; H, 5.06; N, 7.81. Found: C, 60.39; H, 5.11; N, 7.69.

2,7-*endo*-4,6-Oxazatricyclo[6.2.1.$0^{2,7}$]undec-9-ene-3,5-dione (5b): 0.7 g (97%) from 1 g (4 mmol) of **4b**; mp 169-170°C (carbon tetrachloride); IR (KBr) 3280, 1785, 1720 cm^{-1}; ^1H NMR (DMSO - d_6) δ 1.45 (m, 2H, H-11), 3.03 (s, 1H, H-8), 3.30 (s, 1H, H-8), 3.35 (dd, 1H, J = 2.5, 6.5 Hz, H-2), 3.92 (dd, 1H, J = 2.5, 6.5 Hz, H-7), 6.20 (m, 2H, H-9, H-10), 8.40 (br, 1H, NH); HRMS, calcd for $C_9H_9NO_3$ (M^+) 179.0583, found 179.0591.

7-*exo*-Methyl-2,7-*endo*-4,6-oxazatricyclo[6.2.1.$0^{2,7}$]undec-9-ene-3,5-dione (5c): 0.72 (93%) from 1.12 g (4 mmol) of **4c**; mp 174-175°C (carbon tetrachloride); IR (KBr) 3280, 1780, 1730 cm^{-1}; ^1H NMR (DMSO - d_6) δ 1.45 (d, 1H, J = 9.5

Hz, H-11), 1.47 (s, 3H, CH_3), 1.67 (d, 1H, J = 9.5 Hz, H-11), 2.80 (s, 1H, H-1), 3.05 (d, 1H, J = 1.5 Hz, H-2), 3.05 (s, 1H, H-8), 6.24 (m, 2H, H-9, H-10), 8.36 (br, 1H, NH); MS (m/z) 193 (M^+, 6%), 128 (100%); Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 61.90; H, 5.82; N, 7.41.

2,7-*exo*-4,11,6-Dioxazatricyclo[6.2.1.0^{2,7}]undec-9-ene-3,5-dione (5d): 0.66 g (92%) from 1 g (4 mmol) of **4d**; mp 78-79°C (acetone); IR (KBr) 3400, 1780, 1740, 1610 cm^{-1}; ^1H NMR (DMSO - d_6) δ 2.92 (d, 1H, J = 7.5 Hz, H-2), 3.45 (d, 1H, J = Hz, H-7), 4.80 (s, 1H, H-1), 5.15 (s, 1H, H-8), 6.46 (d, 1H, J = 5 Hz, H-9), 6.57 (d, 1H, J = 5 Hz, H-10), 8.60 (br, 1H, NH); MS[21] (m/z) 113 (100%), 69 (87%).

3-*exo*-N-*tert*-butyloxycarbonylaminobicyclo[2.2.1]hept-5-ene-2-*exo*[N-(methoxycarbonylmethyl)]carbamoyl (6a): To a solution of **5a** (0.45 g, 2.5 mmol) in dry THF (10 ml) was added $(Boc)_2O$ (3 mmol) and a few drops of Et_3N; the mixture was stirred at room temperature for 4 h. Glycine methylester (2.5 mmol) in THF (5 ml) was added and stirring was continued for 1 h. After removing the solvent and excess of $(Boc)_2O$, the residue was dissolved in ethyl acetate and washed (water, brine), dried ($NaSO_4$), and concentrated to give 0.65 g (80%) of **6a**; mp 159-160°C (ethyl acetate-petroleum ether); IR (KBr) 3320, 1750, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H, CH_3), 1.50 (m, 1H, H-7), 2.02 (m, 1H, H-7), 2.40 (dd, 1H, J = 1, 8 Hz, H-2), 2.70 (m, 1H, H-1), 2.90 (m, 1H, H-4), 3.80 (s, 3H, CH_3), 3.95 (m, 3H, H-3, CH_2), 5.45 (d, 1H, J = 8Hz, NH), 6.15 (m, 2H, H-5, H-6), 6.45 (br, 1H, NH); HRMS, calcd for $C_{16}H_{24}N_2O_5$ (M^+) 324.1686, found 324.1667.

3-*exo*-N-*tert*-butyloxycarbonylamino-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*[N-(methoxycarbonylmethyl)]carbamoyl (6b): The preparation of dipeptide **6b** was accomplished via a procedure very similar to that described previously (preparation of **6a**). From 0.5 g (2.7 mmol) of **5d** there was obtained 0.7 g (79%) of **6b** as a white solid; mp 127-128°C (ethyl acetate -petroleum ether); IR (KBr) 3340, 1760, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H, CH_3), 2.70 (d, 1H, J = 8 Hz, H-2), 3.65 (s, 3H, CH_3), 3.85 (dd, 2H, J = 6, 8 Hz, CH_2), 4.10 (dd, 1H, J = 8, 10 Hz, H-3), 4.70 (s, 1H, H-1), 5.10 (s, 1H, H-4), 5.80 (d, 1H, J = 10 Hz, NH), 6.35 (m, 2H, H-5, H-6), 6.95 (br, 1H, NH); HRMS, calcd for $C_{15}H_{22}N_2O_6$ (M^+) 326.1479, found 326.1458.

4-Methyl-1,3-oxazine-2,6-dione (7a): The product **5c** (0.5 g, 2.5 mmol) was heated in dry flask at 160°C for 10 min. The dark residue was purified on silica gel column (acetone). After evaporation of the solvent, 0.220 mg (72%) of oxathymine **7a** was obtained as a white powder; mp 174-175°C (Lit.[17] mp 176°C); IR (KBr) 1800, 1700, 1620 cm^{-1}; ^1H NMR ($CDCl_3$ - DMSO - d_6) δ 2.10 (s, 3H, CH_3), 5.40 (s, 1H, H-5), 11.30 (br, 1H, NH); HRMS, calcd for $C_5H_5NO_3$ (M^+) 127.0269, found 127.0281.

1,3-Oxazine-2,6-dione (7b): The product **5d** (0.5 g, 2.7 mmol) was refluxed in dry benzene (40 ml) for 30 min. The solvent and furan were removed under reduced pressure. Chromatography (ether-benzene, 9:1) gave 0.265 g (85%) of oxauracil **7b**; mp 156-158°C (Lit.[11] mp 158.5°C); IR (KBr) 3340, 1800, 1700, 1620 cm^{-1}; ^1H NMR ($CDCl_3$ - DMSO - d_6) δ 5.45 (d, 1H, J = 7 Hz, H-5), 7.25 (dd, 1H, J = 5, 7 Hz, H-4), 11.25 (br, 1H, NH); HRMS, calcd for $C_4H_3NO_3$ (M^+) 113.0113, found 113.0119.

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