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2-Aza-3-Oxabicyclo[2.2.1]heptene Hydrochloride: An Exceptionally Versatile Synthon For Carbocyclic Sugars And Nucleosides

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Abstract: The transformation of cyclopentadiene to 5'-desmethylene 1'-aza carbocyclic sugars has been achieved in four steps: 1. Cycloaddition of chloronitrosocyclohexane to 2-aza-3-oxabicyclo[2.2.1]heptene hydrochloride in EtOH-Et_2O, 2. Nitrogen functionalization, 3. cis hydroxylation and 4. N-O bond cleavage. The protocols provided enable practical access to a range of 5'-desmethylene carbocyclic sugar analogs whose utility has been illustrated with synthesis of a novel 5'-desmethylene analog of aristeromycin.

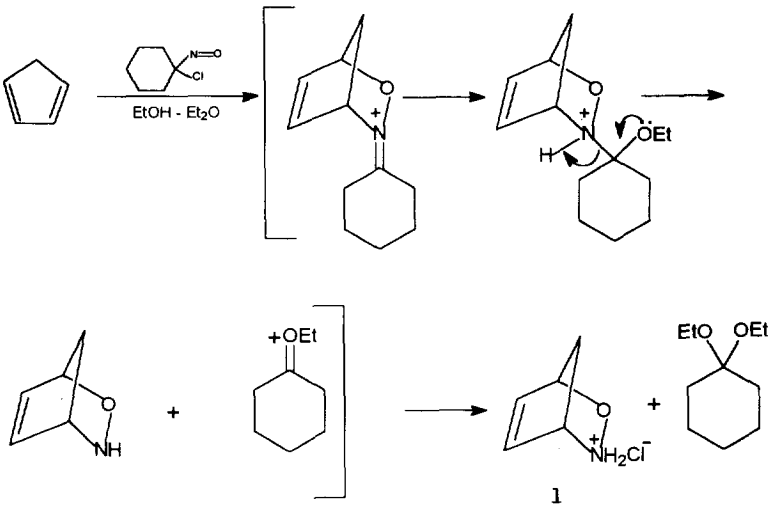
Perhaps the principal reason for the very fruitful outcome of the synthetic endeavors in the carbocyclic nucleosides domain, which has witnessed noteworthy involvement in the very recent past is that a range of cyclopentanoid analogs showed pronounced antiviral activity and thus promised as therapeutically viable agents.[1-4] The interest in carbocyclic analogs of nucleosides came about in a serendipitous manner by the synthesis of aristeromycin,[5] carbovir,[6] neplanocin[7] etc. Simultaneous and rapid developments have brought out the profound antiviral profile exhibited by many of these analogs.[8-12]

Pertinent to the present work is the recent extensive and careful studies which have shown that 5'-desmethylene carbocyclic nucleosides and their analogs can exhibit potent antiviral activity.[13-20]

We illustrate here the noteworthy potential of the easily accessible 2-aza-3-oxabicyclo[2.2.1]heptene hydrochloride **1** for transformation to 5'-desmethylene carbocyclic sugars and nucleosides.

The preparation of compound **1** in a single step from cyclopentadiene was reported by us during endeavours to the synthesis of PG endoperoxide analogs.[21] The reaction of freshly cracked cyclopentadiene with chloronitrosocyclohexane in dry ether-ethanol afforded compound **1** in 94% yields (Scheme-1). Thus batches of 20 g of **1** could be easily prepared by the optimized procedure presented here. Since our first report, numerous batches of **1** have been prepared by us[22] and our experience showed that contamination of the chloronitrosocyclohexane that invariably happens during distillation and the presence of minute amounts of water in ether-ethanol drastically reduced the yield and made the reaction capricious which may explain the earlier unsuccessful attempt to prepare **1** by this procedure.[23] The transformation leading to **1** (Scheme-1) is

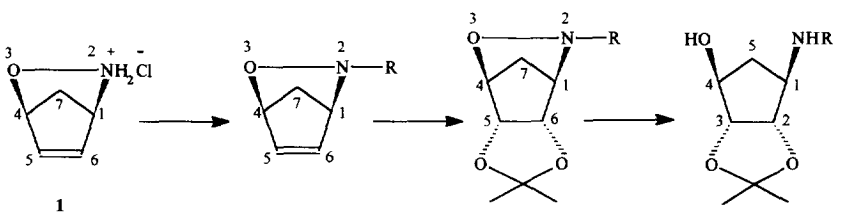
unique. The cyclopentadiene is oxidized at the expense of the nitroso group by a series of carefully regulated steps. The efficient capture of the generated HCl is crucial to the reaction.[24]



1

Scheme - 1

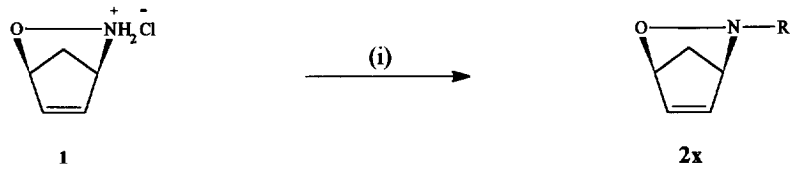
The exceptionally facile approach for the transformation of **1** to the carbocyclic sugars, illustrated in Scheme-2 takes advantage of the basic NH function for the ligand attachment, the strained π bond for cis hydroxylation and the weak N-O bond to release 1' and 4' positions.



1

Scheme-2

The free base, 2-aza-3-oxabicyclo[2.2.1]heptene can be obtained in excellent yields from **1** by neutralization in a biphasic medium having aqueous bicarbonate as one of the layers. However, it is convenient to use *in situ* generated free base for further operations using either aqueous bicarbonate, pyridine or triethylamine. Thus N-acylation of **1** was accomplished in excellent yields to afford **2a** —> **2e** as shown in Scheme-3. A useful variation was the preparation of urea **2f** by the reaction of free base of **1** with carbomethoxysebacoyl isocyanate as described in Scheme-3.



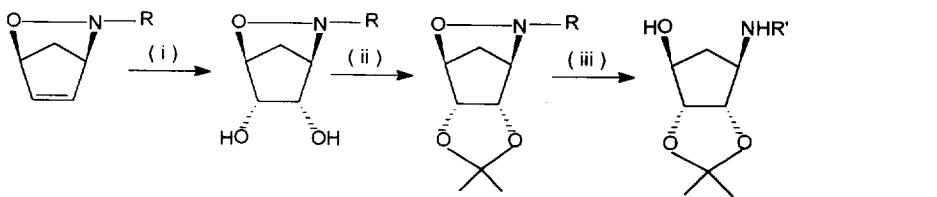
1 2x

2x	R	(i)
2a	$COOCH_2Ph$	Z-Cl, Aq. $NaHCO_3$, 0 °C, 24 h
2b	$COOCH_3$	CH_3OCOCl, Aq. $NaHCO_3$, 0 °C, 24 h
2c	$COOCH_2CH_3$	CH_3CH_2OCOCl, Aq. $NaHCO_3$, 0 °C, 24 h
2d	$COCH_3$	CH_3COCl, Py, PhH, 0 °C, 4 h
2e	$CO(CH_2)_8COOCH_3$	$ClCO(CH_2)_8COOCH_3$, Et_3N, PhH, 0 °C, 3 h
2f	$CONH(CH_2)_8COOCH_3$	$CH_3OCO(CH_2)_8NCO$, PhH, 0 °C, 3 h

Scheme-3

The key step in the transformation of **2** to the carbocyclic sugar framework was the cis hydroxylation. The major consideration here was to achieve this using the readily available permanganate method.[25] Buffered permanganate at -60 °C gave best results in the range of 50% yields. It is recognized that the improvement here is very desirable to make **1** as the most suitable starting material for carbocyclic sugar analogs.

The cis hydroxylation of **2a** —> **2c** was accomplished in ~50% yield in methanol at -60 °C using buffered permanganate (Scheme-4). Although the yields were modest, the products were pure (tlc) and



2 3 4 5

				R	R'
2a	3a	4a	5a	Z	H
2b	3b	4b	5b	$COOCH_3$	$COOCH_3$
2c	3c	4c	5c	$COOCH_2CH_3$	$COOCH_2CH_3$

(i) a. $KMNO_4$ -- $MgSO_4$, -65 °C, MeOH, 0.5h; b. SO_2, -10 °C, 0.5h

(ii) Dry acetone, TsOH, rt, 24h; (iii) Pd(0)/C (5%), H_2, MeOH, 1.5h

Scheme - 4

afforded crystalline isopropylidene derivatives directly. Thus, diols **3a**, **3b** and **3c** were readily transformed into the respective isopropylidene derivatives **4a**, **4b** and **4c** in quantitative yields on treatment with dry acetone in presence of catalytic amounts of p-toluenesulphonic acid at room temperature (Scheme-4).[26]

Compounds **3** (Scheme-4), on their own right can be considered as equivalent to anhydro sugars. The nitrogen substituents here can be further elaborated to afford powerful inhibitors. The strained system here also would be amenable for phosphorylation at the nitrogen location.

The reduction of the N-O bond was carried out, in excellent yields with Pd(0)/C. Our examinations tend to show that earlier report[27] about this reagent affording inconsistent yields in the reduction of the N-O bond, most likely was due to impurities in methanol, the solvent of choice in such operations. In contrast, the initial endeavours to effect metal promoted reduction, which is generally recommended,[28,29] gave poor yields.

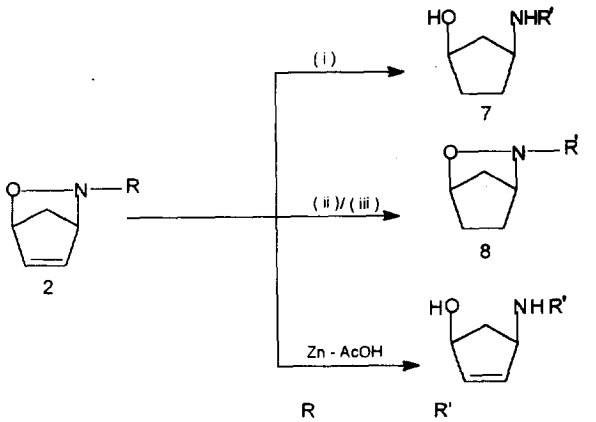
The preparation of **5a** (Scheme-4) in an overall yield of 30% from cyclopentadiene, in our opinion, constitutes, *the most practical approach to this highly versatile synthon.* The transformation of **5a** to pyrimidine carbocycle is presented as one illustration of this aspect (*vide infra*). Yet another interesting feature of **5a** is that it is ideally suited for the preparation of exocyclic amino carbocyclic nucleosides and hydantoins[30] whose syntheses are currently receiving attention. The **4a** —> **5a** change involves the hydrogenolysis of the N-O bond as well as the benzyloxycarbonyl group. Wherever the latter process was not feasible the substituent was retained. Thus, reaction of **4b** and **4c** afforded in excellent yields the urethanes **5b** and **5c** having potential for further elaboration.

Even more facile was the transformation of **1** to 2',3'-dideoxy 5'-desmethylene carbocyclic sugar analogs, a class of compounds which has attracted attention by their ability to terminate nucleic acid synthesis.[1,2] Thus, a two step protocol, involving nitrogen ligand attachment and reduction led to precursors of 2',3'-dideoxy 5'-desmethylene carbocyclic sugar analogs.

As could be seen from Scheme-5, compound **2** arising from ligand attachment to the nitrogen can be programmed to either reduction of the N-O bond as well as the π bond or the π bond alone or exclusively the N-O bond retaining the π system.

The monitoring of the catalytic hydrogenation of **2** showed that the π bond reduction takes place in the first step and then the hydrogenolysis of the N-O bond.[31] This has been taken advantage in the preparation of **8** (Scheme-5) and we have found that this procedure is superior to the diimide reduction, generally employed in such situations.

The transformation of **5a** —> **10** - novel 5'-nor pyrimidine analog of aristeromycin - involving an amino group to uracil change, was accomplished by addition of β-ethoxypropenoyl isocyanate[32] followed by acid mediated cyclization. Thus, addition of β-ethoxypropenoyl isocyanate to **5a** proceeded smoothly to afford, in good yields compound **9** (Scheme-6). Compound **9** underwent cyclization in sulfuric acid to afford **10** in 36% yield Similarly, 1-aminocyclopentane-4-ol **7a** on addition to β-ethoxypropenoyl isocyanate afforded the ureido derivative **11**. Cyclization of **11** to the 5'-nor-2',3'-dideoxy uridine carbocyclic analog **12** was achieved in sulfuric acid.

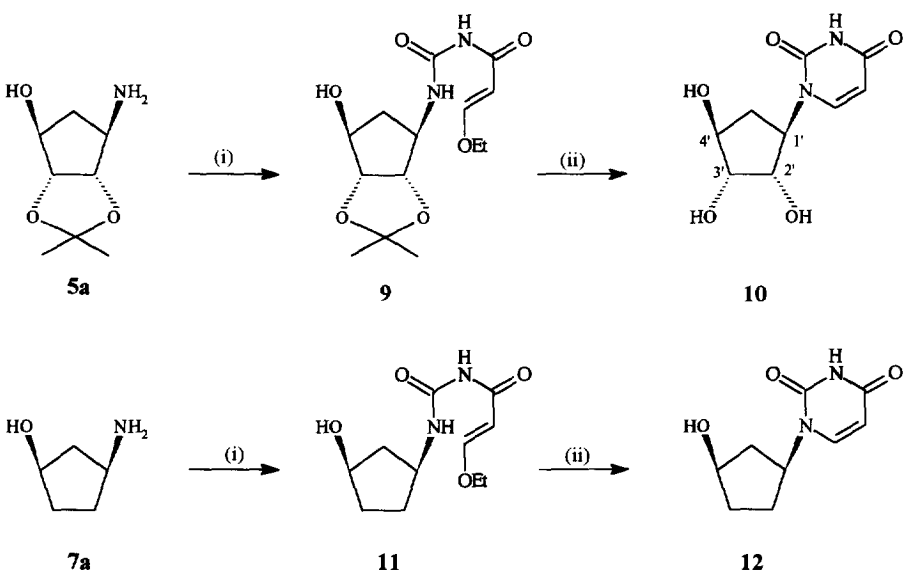


		R	R'
2a	7a	Z	H
2b	7b	$COOCH_3$	$COOCH_3$
2c	7c	$COOCH_2CH_3$	$COOCH_2CH_3$
2b	8b	$COOCH_3$	$COOCH_3$
2c	8c	$COOCH_2CH_3$	$COOCH_2CH_3$
2e	8e	R = R' =	$CO(CH_2)_8COOCH_3$
2f	8f	R = R' =	$CONH(CH_2)_8COOCH_3$

(i) Pd / C (5%), H_2, MeOH, 10 - 14h

(ii) KOOC-N=N-COOK, AcOH, MeOH, 0 °C, 24h

Scheme - 5 (iii) Pd / C (5%), H_2, MeOH, 0.5h



(i) EtOCH=CHCONCO, PhH-DMF, 0 °C, 24 h / CH_2Cl_2 -PhH, 0 °C, 24 h

(ii) 0.5 N H_2SO_4, 60 °C, 0.5 h

Scheme-6

We are hopeful that the readily available **1** would find use in organic synthesis in the coming years.

Experimental

The melting points and boiling points are uncorrected. Infrared spectra were recorded on Perkin Elmer 580/1600 FT instrument either as neat liquid or KBr pellets. ^{1}H NMR spectra were obtained on WP 80 Bruker instrument at 80 MHz and Hitachi R 600 at 60 MHz in $CDCl_3$ unless otherwise stated. The chemical shifts are recorded in ppm with TMS at 0.00 as the internal standard. FAB mass spectra were recorded on a JEOL SX-120/DA-6000 double focusing mass spectrometer with reverse geometry using 6 kv argon beam (10 mA). The accelerating voltage was 10 kev and the spectra were recorded at room temperature with m-nitrobenzyl alcohol as the matrix. Elemental analysis were carried out in automatic C, H, N analysers. Silica gel G (Merck) was used for tlc and column chromatography was done on silica gel (Acme, 100-200 mesh) columns, which were invariably made from a slurry in hexane or benzene. Reactions were monitored whenever possible by tlc. The organic extracts were invariably dried over anhydrous $MgSO_4$ and the solvents evaporated *in vacuo*. Ether and benzene were dried using Na-benzophenone ketyl method. Dry alcohol was prepared by Na-diethyl phthalate method.

2-Aza-3-oxabicyclo[2.2.1]hept-5-ene hydrochloride.[21] (1)

Freshly cracked and dry cyclopentadiene (15.0 g, 230 mmol) was added at once to a stirred and ice cooled solution of chloronitrosocyclohexane[33] [prepared by passing dry chlorine through an etherial solution of cyclohexanone oxime] (5.0 g, 34 mmol), in dry ether (80 mL) and alcohol (15 mL). The reaction mixture was left stirred for 3 h during which the blue color of the reaction mixture completely disappeared. The separated white crystalline hydrochloride was filtered under dry nitrogen atmosphere, washed with ether and dried *in vacuo*. yield : 4.30 g (94%); mp : 82-83 °C. Anal. Calcd. for C_5H_8ClNO (M.W. 133.5): C, 44.94; H, 05.99%. Found : C, 45.19; H, 05.70%. ir : ν_{max} (KBr) cm^{-1}: 3300 (br, NH). ^{1}H nmr (80 MHz, D_2O) δ: 6.95, 6.75 (m, m, 2H, -CH=CH-), 5.75 (br, 1H, 4-H), 5.35 (br, 1H, 1-H), 2.35 (m, 2H, -CHC$\underline{H_2}$CH-).

N-Benzyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]hept-5-ene. (2a)

To an ice cooled and stirred solution of **1**, (3.4 g, 25.4 mmol) in water (250 mL) was added excess of saturated bicarbonate solution till it became basic. Into this was added benzyloxycarbonyl chloride (9.52 mL, 50%, in toluene, equivalent to 28 mmol), dropwise, over 1 h. Cold saturated bicarbonate was added during the course of the reaction to maintain the medium basic. The mixture was left stirred for 24 h, extracted repeatedly with EtOAc (4 x 75 mL) and dried ($MgSO_4$). Evaporation of solvents *in vacuo*, afforded **2a** as a colorless thick liquid that was pure (nmr). yield : 4.70 g, (80%). Anal. Calcd. for $C_{13}H_{13}NO_3$ (M.W. 231): C, 67.53; H,

05.63; N, 06.06%. Found: C, 67.30; H, 06.28; N, 05.90%. ir : ν_{max} (neat) cm^{-1}: 3031, 2960, 1744, 1498, 1454, 1384, 1332. ^1H nmr (80 MHz, $CDCl_3$) δ: 7.31 (m, 5H, C_6H_5-), 6.34 (m, 2H, -CH=CH-), 5.31-5.00 (m, 4H, -$C\underline{H}_2$Ar, 4-H, 1-H), 2.00,1.69 (m, m, 2H, -CHC$\underline{H}_2$CH-). ms : m/z : 232 $(M+H)^+$.

N-Methyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]hept-5-ene. (2b)

To a stirred and ice cooled solution of **1** (1.0 g, 7.46 mmol) in water (25 mL) was added excess of aqueous bicarbonate till it became basic. The free base thus generated was treated with methylchloroformate (0.71 g, 7.5 mmol) over 10 min. The reaction mixture was left stirred for 24 h, extracted with EtOAc (4 x 50 mL), dried and solvents removed *in vacuo* to afford **2b** as a colorless liquid. yield : 0.95 g, (82%). Anal. Calcd. for $C_7H_9NO_3$ (M.W. 155): C, 54.19; H, 05.81; N, 09.03%. Found: C, 54.12; H, 05.71; N, 09.22%. ν_{max} (neat) cm^{-1}: 3560, 3020, 2950, 1720, 1430, 1325, 1180. ^1H nmr (80 MHz, $CDCl_3$) δ: 6.44 (m, 2H, -CH=CH-), 5.22 (br, 1H, 4-H), 5.00 (br, 1H, 1-H), 3.69 (s, 3H, -OCH_3), 2.00,1.69 (m, 2H, -CHC$\underline{H}_2$CH-). ms : (FAB) m/z : 156 $(M+H)^+$.

N-Ethyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]hept-5-ene. (2c)

Compound **2c** was prepared from **1** (3.0 g, 22.4 mmol) and ethylchloroformate (2.4 g, 22.0 mmol) in a manner analogous to the preparation of **2b**; colorless liquid; yield : 3.25 g, (86%). Anal. Calcd. for $C_8H_{11}NO_3$ (M.W. 169): C, 56.81; H, 06.51; N, 08.28%. Found : C, 56.91; H, 06.22; N, 07.95%. ir : ν_{max} (neat) cm^{-1}: 3606, 3453, 2980, 1744, 1708, 1446, 1373. ^1H nmr (80 MHz, $CDCl_3$) δ: 6.44 (m, 2H, -CH=CH-), 5.25 (br, 1H, 4-H), 5.03 (br, 1H, 1-H), 4.19 (q, 2H, -$C\underline{H}_2CH_3$, J=7.5 Hz), 2.00-1.75 (q, 2H, -CHC$\underline{H}_2$CH-), 1.28 (t, 3H, -$CH_2C\underline{H}_3$, J=7.5 Hz). ms : (FAB) m/z : 170 $(M+H)^+$.

N-Acetyl-2-aza-3-oxabicyclo[2.2.1]heptene.[21] (2d)

To an ice cooled and stirred mixture of **1** (1.33 g, 10 mmol) and pyridine (1.18 g, 15 mmol) in dry benzene (25 mL) was added, in drops, a solution of Ac_2O (3.78 g, 37 mmol) in benzene (15 mL). After 4 h, cold saturated $NaHCO_3$ (20 mL, 10%, 22 mmol) was introduced and the mixture left stirred for further 0.5 h. The layers were separated and the aqueous portion extracted with CH_2Cl_2, the combined extracts dried ($MgSO_4$), solvents evaporated and the residue chromatographed over silica gel. Elution with PhH:EtOAc (8 : 2) gave 0.95 g (69%) of **2d** as a colorless liquid. ir : ν_{max} (neat) cm^{-1}: 3019, 2261, 1666 (amide I band), 1376, 849. ^1H nmr (80 MHz, $CDCl_3$) δ 6.56, 6.38 (m, m, 2H, -CH=CH-), 5.31 (m, 2H, 4-H, 1-H), 1.96 (m, 5H, -$COCH_3$, CHC$\underline{H}_2$CH-).

N-Carbomethoxysebacoyl-2-aza-3-oxabicyclo[2.2.1]hept-5-ene. (2e)

To an ice cooled and stirred suspension of **1** (1.2 g, 9.2 mmol) and triethylamine (1.9 g, 18 mmol) in benzene (30 mL) was added, in drops, carbomethoxysebacoyl chloride (2.1 g, 9.2 mmol) in benzene (10 mL) over 0.5 h. After the addition was over, another lot of triethylamine (1.9 g, 18 mmol) was added and the reaction mixture kept stirred for 3 h, washed repeatedly with cold water, dried and solvents evaporated under reduced pressure. The crude product (2 g) was purified by column chromatography using EtOAc:PhH, (1 : 3) to yield 1.6 g, (59%) of **2e**. ir : ν_{max} (neat) cm^{-1}: 2929, 1737, 1668, 1173, 849. ^1H nmr (80 MHz, $CDCl_3$) δ: 6.53, 6.38 (m, m, 2H, -CH=CH-), 5.25 (br, 2H, 4-H, 1-H), 3.65 (s, 3H, $-OCH_3$), 2.25 (m, 4H, $-NCOCH_2-$, $-C\underline{H}_2COOMe$), 2.00-1.00 (m, 14H, $-CH(C\underline{H}_2)_6CH-$, $-CHC\underline{H}_2CH-$). ms : (FAB) m/z : 296 $(M+H)^+$.

N-[N'-Carbomethoxysebacoylaminocarbonyl]-2-aza-3-oxabicyclo[2.2.1]heptene. (2f)

a. 2-Aza-3-oxabicyclo[2.2.1]heptene.

a. A mixture of hydrochloride **1** (1.34 g, 10 mmol) in CH_2Cl_2 (100 mL) and aqueous $NaHCO_3$ (50 mL) was vigorously shaken in a separatory funnel, the CH_2Cl_2 layer separated, dried ($MgSO_4$) and evaporated to give the free base as an yellow oil. yield : 0.99 g, (100%). ir : ν_{max} (neat) cm^{-1}: 3320 (br, NH). ^1H nmr (60 MHz, $CDCl_3$) δ: 6.40-5.88 (m, 2H, -CH=CH-), 4.88 (br, 1H, 4-H), 4.11 (br, 1H, 1-H), 1.50 (m, 2H, $-CHC\underline{H}_2CH-$).

b. To an ice cooled and stirred solution of the free base generated as above, in benzene (15 mL) was added in drops, carbomethoxysebacoyl isocyanate[34] (1.8 g, 8 mmol) in benzene (15 mL). The mixture was stirred for 3 h at 10 °C, solvents evaporated and the crude product chromatographed over silica gel. Elution with EtOAc:PhH (1 : 9) gave 1.50 g (61%) of **2f** as a gum. Anal. Calcd. for $C_{16}H_{26}N_2O_4$ (M.W. 310): C, 61.94; H, 08.39; N, 09.03%. Found : C, 61.48; H, 08.75; N, 09.48%. ir : ν_{max} (neat) cm^{-1}: 3398, 2928, 1737, 1517, 1245, 847. ^1H nmr (80 MHz, $CDCl_3$) δ: 6.42 (m, 2H, -CH=CH-), 5.72 (br, 1H, $-CONHCH_2-$), 5.22 (br, 2H, 4-H, 1-H), 3.72 (s, 3H, $-OCH_3$), 3.22 (m, 2H, $-NHC\underline{H}_2-$), 2.35 (m, 2H, $-C\underline{H}_2COOMe$), 2.10-1.00 (m, 14H, $-CHC\underline{H}_2CH-$, $-CH_2(C\underline{H}_2)_6CH_2-$). ms : (FAB) m/z : 311 $(M+H)^+$.

N-Benzyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]heptane-5,6-diol. (3a)

To a stirred solution of **2a** (5 g, 22 mmol) in methanol (150 mL) at -65 °C, was slowly added, a solution made of $KMnO_4$ (4.4 g, 28 mmol) and $MgSO_4$ (3.4 g, 28 mmol) in distilled water (75 mL) over 0.5 h. It was then allowed to warm upto -10 °C and SO_2 was bubbled to ensure complete reduction of the permanganate. The resulting reaction mixture was filtered, the filtrate concentrated to 25 mL under reduced pressure, extracted with CH_2Cl_2 (2 x 50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to give **3a** as a pure (tlc) gum. yield : 3.20 g, (56%). Anal. Calcd. for $C_{13}H_{15}NO_5$ (M.W. 265): C, 58.86; H, 05.66; N, 05.28%.

Found: C, 58.53; H, 05.63; N, 06.06%. ir : ν_{max} (neat) cm^{-1}: 3409, 3034, 1715, 1455, 1393, 1257, 1094. ^1H nmr (80 MHz, $CDCl_3$) δ: 7.44 (m, 5H, C_6H_5-), 5.19 (s, 2H, -C<u>H</u>$_2$Ar), 4.75-4.00 (m, 4H, 5-H, 6-H, 4-H, 1-H), 2.25-1.56 (m, 4H, 5-OH, 6-OH [exchangeable with D_2O], -CH-C<u>H</u>$_2$-CH-). ms : (FAB) m/z : 266 $(M+H)^+$.

N-Methyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]heptane-5,6-diol. (3b)

To a stirred and previously cooled solution (~ -65 °C) of N-methyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]- heptene **2b** (3.30 g, 21.29 mmol) in methanol (150 mL) was slowly added, a solution made of $KMnO_4$ (3.06 g, 19.4 mmol) and $MgSO_4$ (3.0 g, 24.9 mmol) in distilled water (60 mL) over 0.5 h. The mixture was left stirred for another 0.5 h, allowed to warm upto ~ -10 °C, SO_2 bubbled to ensure the complete reduction of permanganate, filtered, concentrated to ~20 mL, extracted with CH_2Cl_2 (3 x 30 mL), dried and evaporated to give **3b** as a pure (tlc) gum. yield: 1.95 g, (48%). Anal. Calcd. for $C_7H_{11}NO_5$ (M.W. 189): C, 44.44; H, 05.82; N, 07.40%. Found : C, 44.50; H, 06.15; N, 07.27%. ir : ν_{max} (neat) cm^{-1}: 3426, 2961, 1718, 1445, 1340, 1254, 1198, 1095. ^1H nmr (80 MHz, $CDCl_3$) δ: 4.31 (br, 2H, 5-H, 6-H), 4.03 (br, 2H, 4-H, 1-H), 3.91 (s, 3H, -OCH_3), 1.75 (m, 2H, -CHC<u>H</u>$_2$CH-). ms : (FAB) m/z : 190 $(M+H)^+$.

N-Ethyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]heptane-5,6-diol. (3c)

A solution made of $KMnO_4$ (0.93 g, 5.89 mmol) and $MgSO_4$ (0.71 g, 5.89 mmol) in distilled water (40 mL), was added over 0.5 h, to a stirred solution of N-ethyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]heptene **2c** (1 g, 5.9 mmol) in methanol (120 mL) at -60 °C. The reaction mixture was left stirred for another 0.5 h, allowed to reach ~ -10 °C, SO_2 bubbled to ensure the complete reduction of permanganate, filtered, concentrated *in vacuo*, extracted with ether (2 x 40 mL), dried ($MgSO_4$) and solvents evaporated *in vacuo* to give **3c** as a syrup. yield : 0.6 g, (49%). Anal. Calcd. for $C_8H_{13}NO_5$ (M.W. 203): C, 47.29; H, 06.40; N, 06.89%. Found : C, 47.22; H, 06.27; N, 06.50%. ir : ν_{max} (neat) cm^{-1}: 3427, 2958, 1718, 1446, 1337, 1254, 1095, 1063. ^1H nmr (80 MHz, $CDCl_3$) δ: 4.44 (br, 2H, 5-H, 6-H), 4.19 (q, 2H, -C<u>H</u>$_2$CH$_3$), 4.00 (br, 2H, 4-H, 1-H), 3.84 (br, 2H, 6-OH, 5-OH [exchangeable with D_2O)], 2.09-1.75 (m, m, 2H, -CH-C<u>H</u>$_2$-CH-), 1.25 (t, 3H,-CH_2C<u>H</u>$_3$). ms : (FAB) m/z : 204 $(M+H)^+$.

N-Benzyloxycarbonyl-5,6-<u>O</u>-isopropylidene-2-aza-3-oxabicyclo[2.2.1]heptane. (4a)

A solution of **3a** (2 g, 7.6 mmol) in dry acetone (15 mL) and catalytic amount of p-toluenesulphonic acid was kept overnight. The white colorless crystals of **4a** were filtered and dried *in vacuo*. yield : 2.15 g, (93%). mp : 78 °C. Anal. Calcd. for $C_{16}H_{19}NO_5$ (M.W. 305): C, 62.95; H, 06.23; N, 04.59%. Found : C, 62.47; H, 06.68; N, 04.13%. ir : ν_{max} (KBr) cm^{-1}: 3445, 1705, 1211, 1184, 1105, 1055. ^1H nmr (80 MHz, $CDCl_3$) δ:

7.41 (m, 5H, $C_6\underline{H}_5$-), 5.22 (s, 2H, -C$\underline{H}_2$Ar), 4.63 (br, 2H, 5-H, 6-H), 4.31 (br, 2H, 4-H, 1-H), 2.16, 1.69 (m, m, 2H, -CHC$\underline{H}_2$CH-), 1.41, 1.25 (s, s, 6H, -C(CH_3)$_2$). ms : (FAB) m/z : 306 $(M+H)^+$.

N-Methyloxycarbonyl-5,6-O-isopropylidene-2-aza-3-oxabicyclo[2.2.1]heptane. (4b)

Compound **4b** was prepared from **3b** (1.5 g, 7.9 mmol) and dry acetone (20 mL) in presence of catalytic amount of p-toluenesulphonic acid as described for **4a**. yield : 1.44 g, (79%). mp : 120 °C. ir : ν_{max} (KBr) cm^{-1}: 3410, 1715, 1441, 1337, 1208, 1054. ^{1}H nmr (80 MHz, $CDCl_3$) δ: 4.53 (br, 2H, 5-H, 6-H), 4.31 (m, 2H, 4-H, 1-H), 3.78 (s, 3H, -OCH_3), 2.16 (m, 2H, -CHC$\underline{H}_2$CH-), 1.41, 1.25 (s, s, 6H, -C(CH_3)$_2$). ms : (FAB) m/z : 230 $(M+H)^+$.

N-Ethyloxycarbonyl-5,6-O-isopropylidene-2-aza-3-oxabicyclo[2.2.1] heptane. (4c)

Compound **4c** was prepared from **3c** (0.58 g, 2.86 mmol) and dry acetone (10 mL) in presence of catalytic amount of p-toluenesulphonic acid as described for **4a**. yield : 0.7 g, (100%). mp : 59 °C. Anal. Calcd. for $C_{11}H_{17}NO_5$ (M.W. 243): C, 54.32; H, 06.99; N, 05.76%. Found : C, 54.37; H, 06.64; N, 05.96%. ir : ν_{max} (KBr) cm^{-1} 3448, 2989, 1709, 1324, 1209, 1054. ^{1}H nmr (80 MHz, $CDCl_3$) δ: 4.63 (m, 2H, 5-H, 6-H), 4.38 (br, 2H, 4-H, 1-H), 4.25 (q, 2H, -OC$\underline{H}_2$$CH_3$ J=7.5Hz), 2.22, 1.72 (m, m, 2H, -CHC$\underline{H}_2$CH-), 1.56-1.17 (m, 9H, -C(CH_3)$_2$, -CH_2C$\underline{H}_3$). ms : (FAB) m/z : 244 $(M+H)^+$.

1-Amino-2,3-O-isopropylidene dioxycyclopentane-4-ol. (5a)

Compound **4a** (1.5 g, 5.08 mmol) in dry methanol (20 mL) and Pd(0)/C (0.05 g, 5%) was stirred under a positive pressure of hydrogen for 1.5 h, filtered, solvents evaporated *in vacuo* and the crude product crystallized from hot EtOAc. yield : 0.6 g, (70%). mp : 119 °C. Anal. Calcd. for $C_8H_{15}NO_3$ (M.W. 173): C, 55.49; H, 08.67; N, 08.09%. Found : C, 55.42; H, 08.34; N, 08.08%. ir : ν_{max} (KBr) cm^{-1}: 3439, 3344, 3285, 1380, 1207, 1044, 910. ^{1}H nmr (80 MHz, $CDCl_3$) δ: 4.69 (d, 1H, 3-H), 4.41 (d, 1H, 2-H), 4.09 (d, 1H, 4-H), 3.59 (d, 1H, 1-H), 2.60 (m, 3H, -OH, -NH_2), 2.01-1.40 (m, 2H, -CHC$\underline{H}_2$CH-), 1.38, 1.28 (s, s, 6H, -C(CH_3)$_2$). ms : (FAB) m/z : 174 $(M+H)^+$.

N-Methyloxycarbonyl-1-amino-2,3-O-isopropylidene dioxycyclopentane-4-ol. (5b)

A mixture of **4b** (0.9 g, 3.9 mmol) and Pd(0)/C (0.05 g, 5%) in dry methanol (35 mL) was hydrogenated under a positive pressure of hydrogen for 2 h, filtered and solvents evaporated *in vacuo* to afford **5b** as a white solid which was further purified by crystallization from EtOAc. yield : 0.9 g, (100%). mp : 100-102 °C. Anal. Calcd. for $C_{10}H_{17}NO_5$ (M.W. 231): C, 51.95; H, 07.36; N, 06.06%. Found : C, 51.56; H, 07.68; N, 05.83%. ir : ν_{max} (KBr) cm^{-1}: 3380, 2940, 1680, 1500, 1450. ^{1}H nmr (80 MHz, $CDCl_3$) δ: 5.63 (m,

1H, -NHCOOMe), 4.53 (m, 2H, 3-H, 2-H), 4.34 (m, 2H, 4-H, 1-H), 3.72 (s, 3H, $-OCH_3$), 2.47-1.47 (m, 3H, $-CHCH_2CH-$, OH), 1.41, 1.25 (s, s, 6H, $-C(CH_3)_2$). ms : (FAB) m/z : 232 $(M+H)^+$.

N-Ethyloxycarbonyl-1-amino-2,3-O-isopropylidene dioxycyclopentane-4-ol. (5c)

A solution of **4c** (0.6 g, 2.47 mmol) in dry methanol (25 mL) was hydrogenated over Pd(0)/C (0.03 g, 5%) for 45 min. Filtration and evaporation of the solvent gave **5c** as a white powder. yield: 0.54 g, (90%). mp : 97 °C. ir : ν_{max} (KBr) cm^{-1}: 3280, 1690, 1530, 1430, 1310. ^1H nmr (80 MHz, $CDCl_3$) δ: 5.56 (m, 1H, -NHCOOEt), 4.47 (m, 2H, 3-H, 2-H), 4.21 (m, 2H, 4-H, 1-H), 4.10 (q, 2H,-CH_2CH_3), 2.44-1.44 (m, 3H, $-CH_2-$, -OH), 1.44-1.00 (m, 9H, $-C(CH_3)_2$, $-CH_2CH_3$). ms : (FAB) m/z : 246 $(M+H)^+$.

N-Methyloxycarbonyl-5,6-diacetoxy-2-aza-3-oxabicyclo[2.2.1]heptane. (6b)

To an ice cooled and stirred solution of **3b** (0.34 g, 1.82 mmol) in dry benzene (15 mL) was added pyridine (0.5 mL, 6.18 mmol), followed by Ac_2O (0.4 mL, 4.23 mmol). The mixture was left stirred for 24 h, evaporated, and the residue chromatographed over silica gel. Elution with PhH : EtOAc (10%) gave **6b** as a white solid. yield : 0.43 g, (87%). mp : 120 °C. Anal. Calcd. for $C_{11}H_{15}NO_7$ (M.W. 273): C, 48.35; H, 05.49; N, 05.13%. Found: C, 48.06; H, 05.32; N, 05.20%. ir : ν_{max} (KBr) cm^{-1}: 2924, 1753, 1441, 1379, 1297, 1244, 1210, 1074, 1057. ^1H nmr (80 MHz, $CDCl_3$) δ: 5.09 (br, 2H, 5-H, 6-H), 4.63 (br, 2H, 4-H, 1-H), 3.84 (s, 3H, $-OCH_3$), 2.06 (m, 8H, $-OCOCH_3$ x 2, $-CHCH_2CH-$). ms : (FAB) m/z : 274 $(M+H)^+$.

N-Methyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]heptane. (8b)

A mixture of **2b** (0.7 g, 4.46 mmol) and Pd(0)/C (0.05 g, 5%) in dry methanol (50 mL) was stirred under a positive pressure of hydrogen for 0.5 h. Reduction of the double bond occurs with immediate absorption of hydrogen. It was then filtered to remove catalyst. Evaporation of solvents *in vacuo* gave **8b**, along with small amounts of amido alcohol **7b**. Further purification by column chromatography over silica gel using PhH (100%) as eluent gave **8b** as a liquid. yield : 0.65 g, (92%) . ir : ν_{max} (neat) cm^{-1}: 2955, 1712, 1538. ^1H nmr (80 MHz, $CDCl_3$) δ: 4.81 (br, 1H, 4-H), 4.66 (br, 1H, 1-H), 3.88 (s, 3H, $-OCH_3$), 1.88 (m, 6H, $-CHCH_2CH_2CH-$,CH-CH_2-CH-). ms : (FAB) m/z : 158 $(M+H)^+$.

N-Ethyloxycarbonyl-2-aza-3-oxabicyclo[2.2.1]heptane. (8c)

A mixture of **2c** (2.0 g, 11.83 mmol) and Pd(0)/C (0.2 g, 5%) in dry methanol (100 mL) was stirred under a positive pressure of hydrogen for 0.5 h. Catalyst was filtered and solvents evaporated *in vacuo* to give **8c** as a colorless liquid along with small amounts of amido alcohol **7c**. Column chromatography using

PhH (100%) as eluent gave 1.92 g, (95%) of **8c**. Anal. Calcd. for : $C_8H_{13}NO_3$ (M.W. 171): C, 56.14; H, 07.60; N, 08.19%. Found : C, 55.98; H, 07.93; N, 08.12%. ir : ν_{max} (neat) cm^{-1}: 2979, 1744, 1702. ^1H nmr (80 MHz, $CDCl_3$) δ: 4.75 (br, 1H, 4-H), 4.63 (br, 1H, 1-H), 4.22 (q, 2H, -OC<u>H</u>$_2$CH$_3$), 1.75 (m, 6H, -CHC<u>H</u>$_2$C<u>H</u>$_2$CH-, -CHC<u>H</u>$_2$CH-), 1.31 (t, 3H, -OCH$_2$C<u>H</u>$_3$). ms : (FAB) m/z : 172 $(M+H)^+$.

N-Carbomethoxysebacoyl-2-aza-3-oxabicyclo[2.2.1]heptane. (8e)

To an ice cooled and stirred suspension of **2e** (0.21 g, 0.7 mmol) and freshly prepared potassium azodicarboxylate (0.3 g, 1.5 mmol) in dry methanol (10 mL) was added in drops conc. HCl (0.11 mL) in dry methanol (15 mL). The mixture was stirred for 24 h, solvents evaporated without heating, the residue extracted with CH_2Cl_2 (3 x 5 mL), dried ($MgSO_4$) and solvents evaporated to yield **8e**, as a low melting solid. yield : 0.21 g, (99%). mp : 28-30 °C. ir : ν_{max} (neat) cm^{-1}: 3457, 2929, 1737, 1655, 1438. ^1H nmr (80 MHz, $CDCl_3$) δ: 4.86 (m, 2H, 4-H, 1-H), 3.73 (s, 3H, -OCH$_3$), 2.36 (m, 4H, -NCOCH$_2$-, -C<u>H</u>$_2$COOMe), 2.00-0.90 (m, 18H, -CH$_2$(C<u>H</u>$_2$)$_6$CH$_2$-, -CHC<u>H</u>$_2$C<u>H</u>$_2$CH-, -CHC<u>H</u>$_2$CH-). ms : (FAB) m/z : 298 $(M+H)^+$.

N-[N'-Carbomethoxysebacoylaminocarbonyl]-2-aza-3-oxabicyclo[2.2.1] heptane. (8f)

To an ice cooled and stirred suspension of **2f** (0.21 g, 0.68 mmol) and freshly prepared potassium azodicarboxylate (0.3 g, 1.5 mmol) in dry methanol was added in drops conc. HCl (0.11 mL) in dry methanol (15 mL). The reaction mixture was stirred for 24 h, solvents evaporated *in vacuo* without heating, the residue extracted with CH_2Cl_2 (3 x 5 mL), dried ($MgSO_4$), evaporated and chromatographed over silica gel. Elution with PhH : EtOAc (8:2) gave **8f** as a sticky solid. yield : 0.2 g, (96%). Anal. Calcd. for : $C_{16}H_{28}N_2O_4$ (M.W. 312): C, 61.54; H, 08.97; N, 08.97%. Found : C, 61.60; H, 08.89; N, 08.57%. ir : ν_{max} (neat) cm^{-1}: 3432, 3003, 2933, 1731, 1672, 1521, 756. ^1H nmr (80 MHz, $CDCl_3$) δ: 5.92 (br, 1H, -NH), 4.71 (br, 2H, 4-H, 1-H), 3.75 (s, 3H, -OCH$_3$), 3.28 (q, 2H, -NHC<u>H</u>$_2$-), 2.30 (t, 2H, -C<u>H</u>$_2$COOMe), 2.10-1.00 (m, 18H, -CH$_2$(C<u>H</u>$_2$)$_6$CH$_2$-, -CHC<u>H</u>$_2$C<u>H</u>$_2$CH-, -CHC<u>H</u>$_2$CH-). ms : (FAB) m/z : 313 $(M+H)^+$.

1-Aminocyclopentane-4-ol. (7a)

A stirred solution of **2a** (1.0 g, 4.33 mmol) was hydrogenated over Pd(0)/C (0.05 g, 5%) in dry MeOH (25 mL), under a positive pressure of hydrogen, for 14 h, filtered and evaporated to give **7a** as a pure (tlc) gum. yield : 0.42 g, (97%). ir : ν_{max} (neat) cm^{-1}: 3371, 2971. ^1H nmr (80 MHz, $CDCl_3$ + DMSO-d_6) δ: 3.69 (m, 2H, 4-H, 1-H), 1.66 (m, 6H, -CHC<u>H</u>$_2$C<u>H</u>$_2$CH-, -CHC<u>H</u>$_2$CH-). ms : (FAB) m/z : 102 $(M+H)^+$.

N-Methyloxycarbonyl-1-aminocyclopentane-4-ol. (7b)

Compound **7b** was prepared from **2b** (0.76 g, 4.87 mmol) in dry methanol (20 mL) by hydrogenation over Pd(0)/C (0.05 g, 5%) for 10 h. The mixture was filtered and solvents evaporated *in vacuo* to give **7b** as a pure (tlc) gum. yield : 0.72 g, (93%). Anal. Calcd. for $C_7H_{13}NO_3$ (M.W. 159): C, 52.83; H, 08.18; N, 08.81%. Found : C, 53.16; H, 07.94; N, 09.93%. ir : ν_{max} (neat) cm^{-1}: 3312, 2983, 1744, 1704. ^1H nmr (80 MHz, $CDCl_3$) δ: 5.66 (br, 1H, -NHCOOMe), 4.33 (br, 2H, 4-H, 1-H), 3.75 (s, 3H, $-OCH_3$), 2.19-1.59 (m, 6H, $-CHCH_2CH_2CH-$, $-CHCH_2CH-$). ms : (FAB) m/z : 160 $(M+H)^+$.

N-Ethyloxycarbonyl-1-aminocyclopentane-4-ol. (7c)

A stirred solution of **2c** (0.8 g, 4.73 mmol) in dry methanol (25 mL) was hydrogenated over Pd(0)/C (0.05 g, 5%) under a positive pressure of hydrogen for 10 h, filtered, solvents evaporated *in vacuo* to give **7c** as a viscous liquid. yield : 0.8 g, (95%). Anal. Calcd. for $C_8H_{15}NO_3$ (M.W. 173): C, 55.49; H, 08.67; N, 08.09%. Found : C, 55.88; H, 09.06; N, 08.43%. ir : ν_{max} (neat) cm^{-1}: 3328, 2966, 1694. ^1H nmr (80 MHz, $CDCl_3$) δ: 5.31 (br, 1H, -NHCOOEt), 4.37 (m, 2H, 4-H, 1-H), 4.10 (q, 2H, $-OCH_2CH_3$), 2.31-1.50 (m, 6H, $-CHCH_2CH_2CH-$, $-CHCH_2CH-$), 1.25 (t, 3H, $-CH_2CH_3$). ms : (FAB) m/z : 174 $(M+H)^+$.

1-[β-Ethoxypropenoyl]-Ureido-2,3-O-isopropylidene dioxycyclopentane-4-ol. (9)

A solution of β-ethoxypropenoyl isocyanate[32] in benzene (2 mL, 1.05 mmol) was added over a period of 5 min. to a solution of **5a** (0.18 g, 1.05 mmol) in dry CH_2Cl_2 (15 mL) at room temperature. The reaction mixture was stirred for 24 h, solvents evaporated *in vacuo*, extracted with EtOAc (4 x 5 mL), dried and evaporated *in vacuo* leaving **9** as a yellowish powder which was recrystallized from hot EtOAc-ether. yield : 0.175 g, (53%). mp : 210 °C. Anal. Calcd. for $C_{14}H_{22}N_2O_6$ (M.W. 314): C, 53.50; H, 07.01; N, 08.92%. Found : C,53.61; H, 07.45; N,08.62%. ir : ν_{max} (KBr) cm^{-1}: 3306, 3226, 2977, 1699. ^1H nmr (80 MHz, $CDCl_3$) δ: 9.47 (s, 1H, -CONHCO-), 9.16 (d, 1H, -CHNHCO-), 7.59 (d, 1H, $-CH_2O-CH=CH-$, J=12.5Hz), 5.44 (d, 1H, $-CH=CH-CO-$, J=12.5Hz), 4.59 (br, 2H, 3-H, 2-H), 4.28 (br, 2H, 4-H, 1-H), 3.94 (q, 2H, $-CH_2CH_3$), 3.00-1.56 (m, 2H, $-CH-CH_2-CH-$), 1.31 (m, 9H, $-C(CH_3)_2$, $-CH_2CH_3$). ms : (FAB) m/z : 315 $(M+H)^+$.

5'-Nor-uridine Carbocyclic analog. (10)

A stirred suspension of **9** (0.1 g, 0.33 mmol) in dil. H_2SO_4 (1N, 1 mL) was held at 60-65 °C for 0.5 h. The reaction mixture was cooled and neutralized with cold aqueous $NaHCO_3$. The neutral solution was concentrated *in vacuo* to a pasty solid and extracted with hot EtOAc (4 x 5 mL). The combined organic layers were dried (MgSO4) and evaporated *in vacuo* to give **10** as a yellowish gum. yield : 0.026 g, (36%). ir : ν_{max} (neat) cm^{-1}: 3432, 2924, 1694, 1682. ms : (FAB) m/z: 229 $(M+H)^+$.

1-[β-Ethoxypropenoyl]-Ureido cyclopentane-4-ol. (11)

To a stirred and ice cooled solution of **7a** (0.18 g, 1.05 mmol) in dry DMF (1.5 mL) was added, in drops, the acyl isocyanate solution in benzene (1.1 mL, equivalent to 1.05 mmol). The reaction mixture was stirred for 24 h and solvents evaporated in vacuo leaving a gummy compound which was purified by column chromatography over silica gel using EtOAc:MeOH (95:5) as eluent. Recrystallization from EtOAc-MeOH gave **11** as white crystals. yield : 0.15 g, (60%). mp : 150 °C. Anal. Calcd. for $C_{11}H_{18}N_2O_4$ (M.W. 242): C, 54.55; H, 07.44; N, 11.57%. Found : C, 54.68; H, 07.21; N, 12.01%. ir : ν_{max} (KBr) cm^{-1}: 3288, 2968, 1682, 1614, 1548. ^1H nmr (80 MHz, $CDCl_3$) δ: 9.72 (s, 1H, -CONHCO-), 9.13 (d, 1H, -CHNHCO-), 7.66 (d, 1H, $-CH_2$-O-CH=CH-, J=12.5Hz), 5.41 (d, 1H, -CH=CH-CO-, J=12.5Hz), 4.34 (br, 2H, 4-H, 1-H), 3.97 (q, 2H, $-OCH_2CH_3$), 2.19-1.50 (m, 6H, $-CHCH_2CH_2CH$, $-CHCH_2CH$-), 1.31 (t, 3H, $-CH_2CH_3$). ms : (FAB) m/z : 243 $(M+H)^+$.

5'-Nor-2',3'-dideoxy-Uridine Carbocyclic analog. (12)

A solution of **11** (0.07 g, 0.288 mmol) in dil. H_2SO_4 (1N, 1 mL) was held at 60 °C for 0.5 h, cooled and neutralized with cold aqueous $NaHCO_3$ (5 mL). The neutral solution was concentrated to a pasty solid and dried further to remove the last traces of water. The residual solid was extracted with EtOAc (4 x 5 mL) and solvents evaporated *in vacuo* to give **12** as a yellowish gum. yield : 0.028 g, (49%). ir : ν_{max} (KBr) cm^{-1}: 3446, 2367, 1717, 1473, 1395. ^1H nmr (60 MHz, $CDCl_3$) δ: 7.80 (d, 1H, -NCH=CH-), 5.80 (d, 1H, -CH=CHCO-), 5.20 (m, 1H, 4'-H), 4.50 (m, 1H, 1'-H), 2.00 (m, 6H, $-CHCH_2CH_2CH$-, $-CHCH_2CH$-). ms : (FAB) m/z : 197 $(M+H)^+$.

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