A simple synthesis of 5-spirobarbituric acids and transformations of spirocyclopropanobarbiturates to 5-substituted barbiturates

Palwinder Singh* & Kamaldeep Paul

Department of Chemistry, Guru Nanak Dev University, Amritsar 143 005, India

e-mail: palwinder_singh_2000@yahoo.com

The reactions of barbituric acid and its 1,3-dimethyl derivative with 1,2-dibromoethane, 1,4-dibromobutane, 1,5-dibromopentane and 1,2-bis[bromomethyl] benzene in DMF-K_2CO_3 (base), $TBAHSO_4$ (catalyst) provide 5-spirobarbiturates as major products along with other products. The 5,7-dimethyl-5,7-diaza-spiro[2.5]octane-4,6,8-trione undergoes ring opening with ^-CN, ^-SR and Br_2 to provide 5-substituted barbiturates.

5-Substituted barbiturates have been predominantly used for their anticonvulsant[1] and sedative-hypnotic[2,3] properties. 5-Monoalkylated barbituric acids like 5-(benzyloxy)benzyl barbituric acids are used in the treatment of cancer and AIDS via inhibition of human uridine phosphorylase (Urd Pase)[4]. 5-Arylidine-1,3-dimethylbarbiturates behave as phototypes of NAD and FAD and cause oxidation of alcohols and thiols to carbonyl compounds and disulfides respectively[5]. Moreover, 5-monosubstituted barbituric acids are the versatile synthons for procuring the C-5 substituted antiviral drugs. 5,5-Disubstituted barbituric acids do play a significant role as sedative and stimulant agents[6]. Equivalent to 5,5-dialkylated barbituric acids, are the compounds in which the C-5 of barbituric acid forms part of the cycloalkane ring present at C-5. This class of barbituric acid based spiro compounds, exihibit anticonvulsant[7], narcotic and analgesic properties[8] and act as dihydroorotate dehydrogenase inhibitors[9].

Literature reports the synthesis of various 5-mono-alkylated barbituric acids by the reaction of monoalkyl malonic esters with urea[10], by the reaction of barbituric acid with aldehydes[4,11]/α,β-unsaturated ketones[12] or by using 5-acylbarbituric acids as synthons[13]. 5,5-Disubstituted barbituric acids are prepared by the condensation of substituted diethyl-malonic esters and urea in the presence of a base[6] and by the palladium catalyzed asymmetric allylic alkyla-

tion of barbituric acids[14]. The synthesis of spiro-barbiturates involves the condensation of 1,1-cyclo-alkanedicarboxylate diester and urea in the presence of a base[7,9,15]. However, in these reports for the synthesis of spirobarbituric acids, the yields are low, especially in the case of spirocyclopropano-barbiturate. In almost all the literature reports for the preparation of barbituric acid based spiro compounds, the reaction involves first the synthesis of substituted malonates followed by condensation with urea. Herein, we report the synthesis of spiro[2.5], spiro[4.5], spiro[5.5]barbituric acids in a single step reaction of commercially available barbituric acid and its 1,3-dimethyl derivative with respective dihaloalkanes under phase transfer catalytic conditions. The spiro[2.5]barbituric acid undergoes ring opening reactions with nucleophiles (-CN, -SR) and electrophiles (Br_2) to provide respective C-5 substituted barbituric acids.

Barbituric acid **1** (R=H) on reaction with dibromoethane in DMF using K_2CO_3 as base and $TBAHSO_4$ (Tetrabutylammonium hydrogen sulphate) as catalyst gave a solid compound (50% of the consumed barbituric acid) while 20% barbituric acid was recovered unchanged. The solid compound (M^+ m/z 154), m.p. 320°C (lit[15] m.p. 320-25°C) has been assigned structure **2d**. Earlier this compound[15] has been synthesized only in 10% yield where 1,1-cyclopropanedicarboxylic diester is condensed with

urea in the presence of a base which might be leading to the cyclopropane ring opening before condensation with urea. Therefore the dialkylation with alkyl dihalides at C-5 of barbituric acid provides an alternative method for procuring spirocyclopropano-barbiturate in higher yield. Under similar reaction conditions 1,3-dimethylbarbituric acid (**1**, R=CH$_3$) on reaction with dibromoethane gave a white solid (70% of consumed barbituric acid), m.p. 265-67°C and 30% starting barbituric acid is recovered unchanged. In ^{1}H NMR spectrum, it shows a 4H singlet at δ 2.23 and a 6H singlet at δ 3.22. In ^{13}C NMR spectrum, it shows a CH$_2$ at 27.86, CH$_3$ at 28.96, C$_5$ quaternary carbon at 48.76, carbonyl carbons at 150.8 and 171.71. ^{1}H and ^{13}C NMR spectra corroborate a symmetrical structure **2a** for this compound (**Scheme I**).

Similarly, **1** (R=H, CH$_3$) on reaction with 1,4-dibromobutane gave spiro[4.5]barbituric acids **2b** and **2e** and reaction with 1,2-bis[bromomethyl]benzene provided compounds **3a** and **3b** [compound **4b** (20%) is formed in case of 1,3-dimethylbarbituric acid]. Reaction of **1** (R=H, CH$_3$) with 1,5-dibromopentane under same reaction conditions gave spiro barbi-turates **2c** and **2f**. In this way, the reactions of barbituric acids with dihaloalkyl-/arylhalides provide a synthetic methodology for the preparation of spiro barbiturates in good yields in a single step reaction. The reactivity behaviour of **1** towards 1,3-dibromo-propane is quite different where instead of the formation of spiro compounds, pyranopyrimidines are formed. **1** (R=H) on reaction with 1,3-dibromo-propane gave two products: 25%, M$^+$ (m/z) 168, m.p. 178°C and 22%, M$^+$ (m/z) 209, m.p. 204°C. The compound with m.p. 178°C shows a 2H quintet at

δ 2.33, 2H triplets at δ 4.02 and 4.49 and 1H singlet at δ 5.52 in ^{1}H NMR spectrum. From this spectral data along with ^{13}C NMR spectrum, this compound has been assigned structure **5** (**Scheme II**). The second compound with m.p. 204°C shows 2H quintets at δ 1.99 and 2.21, 2H triplets at δ 2.46, 3.42, 4.00 and 4.36 in ^{1}H NMR spectrum. It seems as if two dibromopropane units are introduced to the barbituric acid. ^{1}H NMR spectrum along with ^{13}C NMR spectrum corroborates structure **6** (two isomeric forms are possible) for this compound (**Scheme II**).

The expected compound **7** (R=H) is not formed from this reaction. Similarly, **1** (R=CH$_3$) on reaction with 1,3-dibromopropane gave a solid product (60%), m.p. 122°C which in its ^{1}H NMR spectrum shows a 2H quintet at δ 1.98, 2H triplet at δ 2.48, 3H singlets at δ 3.34, and 3.35 and a 2H triplet at δ 4.35. The downfield triplet at δ 4.35 seems to be due to a methylene group linked to oxygen. In ^{13}C NMR spectrum, the C-5 quaternary carbon has been shifted downfield in comparison to C-5 of compound **2a**. From this spectral data, the structure **8** has been assigned to this compound and again the expected compound **7** (R=CH$_3$) is not formed (**Scheme II**). The non-formation of compound **7** may be attributed to the preferred formation of six membered ring over the four membered ring. The reaction time, percentage yields and the melting points of all the spiro compounds are given in **Table I**.

The ^{1}H NMR spectrum of 1, 3-dimethylbarbituric acid shows two proton signal at δ 3.2 along with six protons corresponding to CH$_3$ groups. The complete absence of olifinic proton of C-5 indicates the existence of this barbituric acid in triketo-form **1**
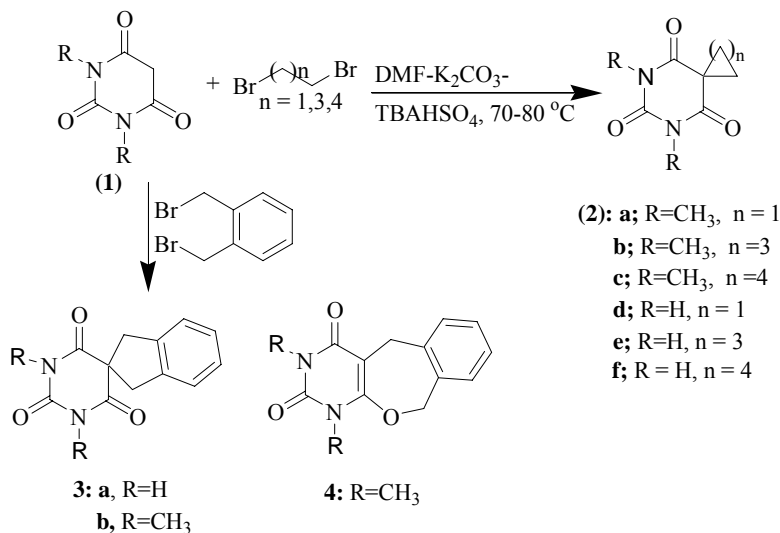
Scheme I
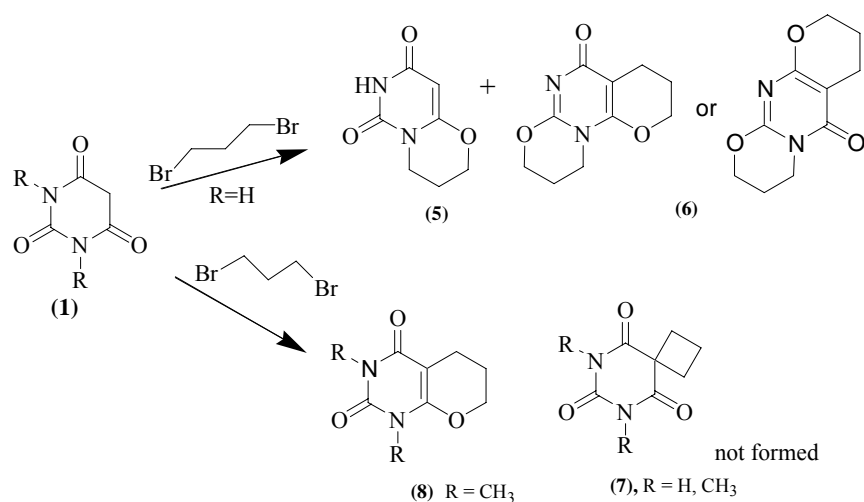
Scheme II

(ref. 16). All the dihalides studied here react first at C-5 of 1,3-dimethylbarbituric acid. The second alkylation also takes place at C-5 except in case of dibromopropane where the preferred formation of six membered ring over four membered ring gives compound **8** instead of **7**. The 1,3-unsubstituted barbituric acid **1** (R=H) also exists in triketo form[16,17] in polar solvents like DMF, DMSO and the C-alkylations are preferred over N-alkylations[17]. In the reactions of **1** (R=H) with dihalides all the reactions take place first at C-5 followed by the second alkylation also at C-5 except in case of dibromopropane where the second alkylation results in formation of six membered ring (**6**) rather than four membered. In case of dibromopropane, the C-alkylation is also plagued by N-alkylation giving unusual products **5** and **6**.

The cyclopropane ring present at C-5 of spirobarbiturates (**2a** and **2d**) is important because of its reactivity pattern equivalent to carbon-carbon double bond. **2a** decoulourizes bromine water. **2a** on reaction with nucleophiles like thiophenol, NaCN and Br$_2$ provide compounds **9(a-c)** (**Scheme III**).

All the new compounds have been characterized by ^{1}H NMR, ^{13}C NMR and mass spectra and elemental analysis. The formation of compound **9a** paves the way for these compounds to act as thymidylate synthase inhibitors.

It is concluded that a synthetic methodology (in better yields relative to literature reports) has been developed for the spirobarbiturates except the formation of compounds **7** where the preferred formation of six membered rings over four membered rings leads to the formation of pyranopyrimidines. In

Table I — Rx time, percentage yield and melting points of spirobarbiturates

Compd	Reaction time (hr)	Yield* (%)	m.p. °C
2a	15	70	265-67
2b	13	52	87
2c	15	31	60
2d	20	70(lit.[18],10%)	320 (dec.)
2e	24	50	259(lit.[18] 258)
2f	20	55	274(lit.[18] 270-73)
3a	15	60	280
3b	13	60	120
5	12	25	178
6	12	22	204
4(R=CH$_3$)	13	20	105
8	12	60	122

* The yields are in terms of consumed barbituric acids

Scheme III

9, a, X = H, Nu = SPh,
b, X = H, Nu = CN,
c, X = Br, Nu = Br
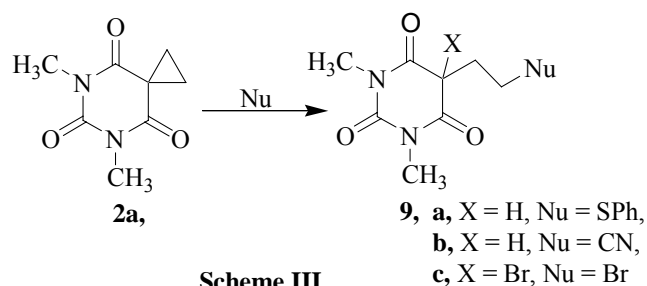
spirobarbiturates **2a** and **2d** the reactivity of cyclopropane ring helps in the synthesis of C-5 substituted barbituric acids which otherwise are not possible because the C-5 alkylation of barbituric acids is always plagued by dialkylation.

Experimental Section

Melting points were determined in capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra in CDCl$_3$/DMSO-d_6 were run on JEOL JNM-AL FT NMR 300 MHz and 75 MHz spectrometer respectively using TMS as an internal standard (chemical shifts in ppm). Column chromatography was performed on silica gel (60-120 mesh) using ethyl acetate-hexane as eluents. Mass spectra were recorded at Electrospray Ionization Interface in the +ve mode. C,H,N analysis were recorded at CDRI, Lucknow.

General method for synthesis of compounds 2a-f, 3a,b, 4, 5, 6 and 8

Equivalent amount of barbituric acid and dibromo-ethane were stirred at 70-80°C in DMF using K$_2$CO$_3$ (2 equivalents) as base and TBAHSO$_4$ as catalyst. The reaction was monitored by TLC and after the completion, it was filtered and solvent removed under reduced pressure. The residue was purified by column chromatography to get the final product and recrystallized from ethanol. The yields are reported with respect to consumed barbituric acid.

5, 7-Dimethyl-5, 7-diaza-spiro[2.5]octane-4, 6, 8-trione 2a: Whitish solid, yield 70%, m.p. 265-67°C; ^{1}H NMR (CDCl$_3$): δ 2.23 (4H, s, 2×CH$_2$), 3.22 (6H, s, N-CH$_3$); ^{13}C NMR: δ 27.8 (-ve, CH$_2$), 28.9 (+ve, N-CH$_3$), 48.8 (C-5), 150,8 (C-2), 171.7 (C-4,C-6).

7, 9-Dimethyl-7,9-diaza-spiro[4.5]decane-6,8,10-trione 2b: Whitish solid, yield 52%, m.p. 87°C; ^{1}H NMR (CDCl$_3$): δ 1.93 (4H, t, J=6.6 Hz, 2xCH$_2$), 2.22 (4H, t, J=6.6 Hz, 2×CH$_2$): 3.31 (6H, s, N-CH$_3$); ^{13}C NMR: δ 27.4 (-ve, CH$_2$), 28.9 (+ve, N-CH$_3$), 39.2 (-ve, CH$_2$), 56.6 (C-5), 151.5 (C-2), 173.4 (C-4, C-6); Anal. Calcd for C$_{10}$H$_{14}$N$_2$O$_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 56.67; H, 7.85; N, 12.19%; MS: m/z 212 (M$^+$+1).

2,4-Dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5-trione 2c: Whitish solid, yield 31%, m.p. 60°C; ^{1}H NMR (CDCl$_3$): δ 1.51-1.60 (2H, m, CH$_2$), 1.67-1.84 (4H, m, 2×CH$_2$), 1.96 (4H, t, J=6.4 Hz, 2×CH$_2$) 3.30 (6H, s, N-CH$_3$); ^{13}C NMR: δ 21.2 (-ve, CH$_2$), 24.5 (-ve, CH$_2$), 28.8 (+ve, N-CH$_3$), 32.7 (-ve, CH$_2$), 50.7 (C-5), 161 (C-2), 172.4 (C-4,C-6); MS: m/z 224.

5,7-Diaza-spiro[2.5]octane-4,6,8-trione 2d: Whitish solid, yield 70%, m.p. 320°C (dec.); ^{1}H NMR (CDCl$_3$+DMSO-d_6): δ 2.26 (4H, s, 2×CH$_2$); ^{13}C NMR: δ 28.2 (-ve, CH$_2$), 47.8 (C-5), 151.9 (C-2), 171.7 (C-4,C-6).

7, 9-Diaza-spiro[4.5]decane-6, 8, 10-trione 2e: Whitish solid, yield 50%, m.p. 259°C, ^{1}H NMR (CDCl$_3$+DMSO-d_6): δ 1.95 (4H, m, 2×CH$_2$), 2.24 (4H, t, J=6.6 Hz, 2×CH$_2$); ^{13}C NMR: δ 28.0 (-ve, CH$_2$), 39.6 (-ve, CH$_2$), 57.0 (C-5), 160 (C-2), 174.1 (C-4,C-6).

2,4-Diaza-spiro[5.5]undecane-1,3,5-trione 2f: Whitish solid, yield 55%, m.p. 274°C, ^{1}H NMR (CDCl$_3$+DMSO-d_6): δ 1.56-1.65 (2H, m, CH$_2$), 1.72-1.83 (4H, m, 2×CH$_2$), 1.98 (4H, t, J=6.4 Hz, 2×CH$_2$); ^{13}C NMR: δ 21.7 (-ve, CH$_2$), 25.0 (-ve, CH$_2$), 33.8 (-ve, CH$_2$), 52.1 (C-5), 162.4 (C-2), 172.8 (C-4,C-6).

[2.3]Benzo-7,9-diaza-spiro[4.5]decane-6,8,10-trione 3a: Whitish solid, yield 60%, m.p. 280°C; ^{1}H NMR (CDCl$_3$+DMSO-d_6): δ 3.73 (4H, s, 2×CH$_2$), 7.25-7.36 (4H, m, Ph); ^{13}C NMR: δ 44.2 (-ve, CH$_2$), 55.9 (C-5), 124.0 (+ve, ArCH), 127.8 (+ve, ArCH), 128 (ArC), 150.9 (C-2), 175.3(C-4,C-6).

[2.3]Benzo-7,9-dimethyl-7,9-diaza-spiro[4.5]decane-6,8,10-trione 3b: Whitish solid, yield 60%, m.p. 120°C; ^{1}H NMR (CDCl$_3$): δ 3.33 (6H, s, N-CH$_3$), 3.61 (4H, s, 2×CH$_2$), 7.20-7.26 (4H, m, Ph); ^{13}C NMR: δ 29.0 (+ve, N-CH$_3$), 44.2 (-ve, CH$_2$), 56.1 (C-5), 124.0 (+ve, ArCH), 127.3 (+ve, ArCH), 127.9 (ArC), 151.4 (C-2), 172 (C-4,C-6). Anal. Calcd for C$_{14}$H$_{14}$N$_2$O$_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.08; H, 5.78; N, 10.83%; MS: m/z 258.

1, 3-Dimethyl-1H, 5H, 10H-11-oxa-1, 3-diaza-dibenzo[a,b]cycloheptene-2,4-dione 4: Whitish solid, yield 20%, m.p. 105°C; ^{1}H NMR (CDCl$_3$): δ 3.35 (3H, s, N-CH$_3$), 3.39 (3H, s, N-CH$_3$), 4.07 (2H, s, CH$_2$), 5.49 (2H, s, O-CH$_2$), 7.33-7.38 (4H, m, Ph); ^{13}C NMR: δ 27.4 (-ve, CH$_2$), 29.0 (+ve, N-CH$_3$), 29.5 (+ve, N-CH$_3$), 72.5 (-ve, CH$_2$), 89.7 (C-5), 127.4 (+ve, ArCH), 128.6 (+ve, ArCH), 128.7 (+ve, ArCH), 130.3 (ArC), 150.6 (C-2), 158.3 (C-4), 164.5 (C-6). Anal. Calcd for C$_{14}$H$_{14}$N$_2$O$_3$: C, 65.11; H, 5.46; N, 10.85. Found: 65.78; H, 5.98; N, 11.10%; MS: m/z 258.

3, 4-Dihydro-2H-pyrimido[6, 1-b][1, 3]oxazine-6,8-dione 5: Whitish solid, yield 25%, m.p. 178°C; ^{1}H NMR (CDCl$_3$+DMSO-d_6): δ 2.20-2.39 (2H, m, CH$_2$), 4.04 (2H, t, J=6.1 Hz, N-CH$_2$), 4.51 (2H, t, J=5.4 Hz, O-CH$_2$), 5.52 (1H, s, C-5H); ^{13}C NMR: δ 20.2 (-ve, CH$_2$), 40.8 (-ve, N-CH$_2$), 67.6 (-ve, O-CH$_2$), 82.0 (+ve, C-5), 152 (C-2), 163.9 (C-4), 172.2 (C-6).

3, 4, 7, 8-Tetrahydro-2H, 6H-1, 5-dioxa-4a, 10-diaza-phenanthren-9-one 6: Whitish solid, yield 22%; m.p. 204°C; ^{1}H NMR (CDCl$_3$): δ 1.93-2.04 (2H, m, CH$_2$), 2.14-2.28 (2H, m, CH$_2$), 2.46 (2H, t, J=6.3

Hz, CH_2), 3.41 (2H, t, J=6.6 Hz, N-CH_2), 4.01 (2H, t, J=6.8 Hz, O-CH_2), 4.40 (2H, t, J=5.1 Hz, O-CH_2); ^{13}C NMR: δ 16.8 (-ve, CH_2), 20.5 (-ve, CH_2), 28.6 (-ve, CH_2), 29.5 (-ve, N-CH_2), 40.6 (-ve, O-CH_2), 70.2 (-ve, O-CH_2), 87.4 (C-5), 149.3 (C-2), 158.4 (C-4), 164.6 (C-6).

1, 3-Dimethyl-1*H*, 5*H*-6, 7-dihydro-pyrano[2, 3-*d*]pyrimidine-2,4-dione 8: Whitish solid, yield 60%; m.p. 122°C; ^{1}H NMR (CDCl$_3$): δ 1.92-2.04 (2H, m, CH_2), 2.48 (2H, t, J=6.4 Hz, CH_2), 3.34 (3H, s, N-CH_3), 3.36 (3H, s, N-CH_3), 4.35 (2H, t, J=5.2 Hz, O-CH_2); ^{13}C NMR: δ 17.5 (-ve, CH_2), 21.1 (-ve, CH_2), 27.8 (+ve, N-CH_3), 28.3 (+ve, N-CH_3), 69.4 (-ve, O-CH_2), 86.9 (C-5), 151 (C-2), 155.9 (C-4), 163.2 (C-6).

General method for synthesis of compounds 9a-c

A mixture of **2a** and the appropriate nucleophile viz. PhSH, NaCN, Br$_2$ was taken in ethanol and heated at 50-60°C for 8-10 hr. The solvent was evaporated and the impure compound purified by column chromatography using ethyl acetate-hexane as eluents.

1,3-Dimethyl-5-(2-phenylsulfanyl-ethyl)-1*H*-pyrimidine-2,4,6-trione 9a: Yellowish oil, yield 55%; ^{1}H NMR (CDCl$_3$): δ 3.24 (3H, s, N-CH_3), 3.29 (3H, s, N-CH_3), 3.30 (2H, t, J=6.3 Hz, CH_2), 4.16 (2H, t, J=5.8 Hz, S-CH_2), 5.01 (1H, s, C-5H), 7.27-7.39 (5H, m, Ph); ^{13}C NMR: δ 27.8 (+ve, N-CH_3), 28.9 (+ve, N-CH_3), 32.6 (-ve, CH_2), 68.6 (-ve, S-CH_2), 78.3 (+ve, C-5H), 127.4 (+ve, ArCH), 129.3 (+ve, ArCH), 130.9 (+ve, ArCH), 134.0 (ArC), 160.0 (C-2), 163.1 (C-4,C-6); MS: m/z 292.

3-(1,3-Dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-propionitrile 9b: Yellowish oil, yield 52%; ^{1}H NMR (CDCl$_3$): δ 2.28 (2H, t, J=6.0 Hz, CH_2), 3.33 (3H, s, N-CH_3), 3.37 (3H, s, N-CH_3), 3.42 (2H, t, J=6.4 Hz, CH_2), 5.11 (1H, s, C-5H), ^{13}C NMR: δ 24.0 (-ve, CH_2), 27.8 (+ve, N-CH_3), 28.7 (+ve, N-CH_3), 32.2 (-ve, CH_2), 78.1 (+ve, C-5), 160.4 (C-2), 163.4 (C-4,C-6); MS: m/z 209.

5-Bromo-5-(2-bromoethyl)-1,3-dimethylpyrimidine-2,4,6-trione 9c: Yellowish oil, yield 60%; ^{1}H NMR (CDCl$_3$): δ 3.20 (2H, t, J=8 Hz, CH_2), 3.40 (6H, s, N-CH_3), 3.45 (2H, t, J=8 Hz, CH_2); ^{13}C NMR: δ 26.7 (-ve, CH_2), 29.5 (+ve, N-CH_3), 30.1 (+ve, N-CH_3), 37.6 (-ve, CH_2), 79.0 (+ve, C-5), 149 (C-2), 165.5 (C-4), 168.7 (C-6); MS: m/z 342.

References

1 Goodman L S & Gilman A, *The Pharmacological basis of therapeutics*, (Mc Graw-Hill, New Delhi), **1991**, 358.
2 Andrews G, *Medical Pharmacology*, (The CV Mosby Co., Saint louis), **1976**, 243.
3 Foye W O, *Principles of Medicinal Chem*, (Lea & Febiger, London), **1989**, 159.
4 Guerin D J, Mazeas D, Musale M S, Naguib F N M, Safarjalani O N A, Kouni M H & Panzica R P, *Bioorg Med Chem Lett*, 9, **1999,** 1477 and references cited therein.
5 a) Meissuer J W G, van der Lean A C & Pandit U K, *Tetrehedron Lett*, 35 (11), **1994**, 2757.
   b) Tanaka K, Chen X & Yoneda F, *Tetrahedron*, 44(11), **1988**, 3241.
6 Cain C K & Kleis J, *J Med Pharm Chem*, 1 (1), **1959**, 31 and references cited therein.
7 Osman A N, Kandeel M M, Said M M & Ahmad E M, *Indian J Chem*, 35B, **1996**, 1073.
8 Cope A C, Kovacic P & Burg M, *J Am Chem Soc*, 71, **1949**, 3656.
9 Fraser W, Suckling C J & Wood H C S, *J Chem Soc*, 11, **1990**, 3137.
10 Cope A C, Heyl D, Peck D, Eide C & Arroyo A, *J Am Chem Soc*, 63, **1941**, 356.
11 Neumann D M, Jursic B S & Martin K L, *Tetrahedron Lett*, 42, **2002**, 1603.
12 El Zoorab M M A & Mogib M A, *Tetrahedron*, 52 (30), **1996**, 10147.
13 a) da Silva E T & Lima E L S, *Tetrahedron Lett*, 44, **2003**, 3621.
   b) Jursic B S & Neumann D M, *Tetrahedron Lett*, 42, **2001**, 4103.
   c) Jursic B S & Stevens E D, *Tetrahedron Lett*, 44, **2003**, 2203.
   d) Jursic B S & Neumann D M, *Tetrahedron Lett*, 42, **2001**, 8435.
14 a) Brunner H, Deml I, Dirnberger W, Ittner K-P, Reiber W & Zimmermann M, *Eur J Inorg Chem*, **1999**, 51-59.
   b) Trost B M & Schroeder G M, *J Org Chem*, 65, **2000**, 1569.
   c) Brunner H, *Chirality*, 13 (8), **2001**, 420.
   d) Brunner H, Stefaniak S & Zabel M, *Synthesis*, 10, **1999**, 1776.
15 McKoown R H & Prankerd R J, *J Chem Soc, Perkin Trans-II*, **1981**, 481.
16 Jovanovic M V & Biehl E R, *J Heterocycl Chem*, 24, **1987**, 191.
17 Katritzky A R & Rees C W, *Comprehensive Heterocyclic Chemsitry*, 3, **1984**, 68.