A Practical Approach for Spiro- and 5-Monoalkylated Barbituric Acids

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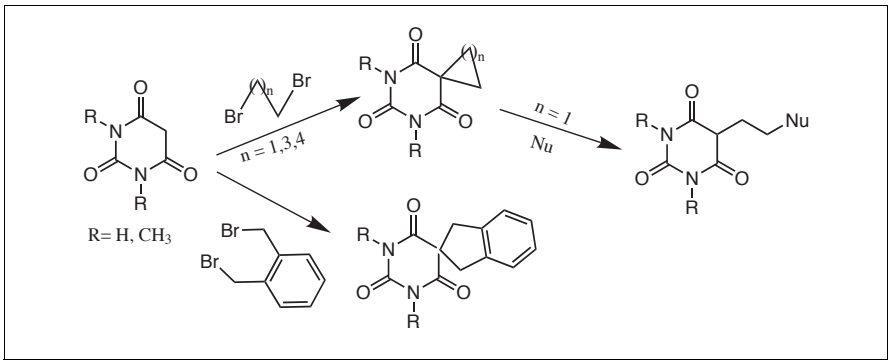

The single step reactions of N,N'- substituted/-unsubstituted barbituric acids with various alkyl dihalides under phase transfer catalytic conditions using DMF–K_2CO_3 (base), $TBAHSO_4$ (catalyst) provide spirobarbituric acids in moderate to high yields. Irrespective of the existence of C_5-monoalkylated compounds in the enolic form (confirmed by the isolation of some of its analogues), the second alkylation predominantly takes place at C_5. The underlying mechanism for the reaction is discussed. The 5,7-dimethyl-5,7-diaza-spiro[2.5]octane-4,6,8-trione undergoes ring opening with NaCN, PhSH, $HS(CH_2)_2OH$ and Br_2 to provide 5-monoalkylated barbiturates which are otherwise difficult to prepare by the usual alkylation of barbituric acids.

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Barbituric acid owes its significance due to similar type of H-bonding as thymine in the biological systems and its presence in many pharmaceutically important molecules [1]. The spirobarbiturates, exhibiting the characteristic feature of conformation locking [2] (common in spiro compounds), are biologically important molecules used as anticonvulsant [3], narcotic and analgesic agents [4], as dihydroorotate dehydrogenase inhibitors [5] and in the construction of modified oligonucleotides [6].

The widespread applications of barbituric acid based spiro compounds in biology and their use as synthons for C_5-monosubstituted barbituric acids prompted us to develop a simple synthetic methodology for spirocycloalkylbarbituric acids. A few reports for the synthesis of spirocycloalkylbarbituric acids are available which involve the condensation of 1,1-cycloalkanedicarboxylate diester and urea in the presence of a base [3,5,7]. However, these reactions mainly suffer from low yields, especially in the case of spirocyclopropanobarbiturate (10%). The available routes for procuring 5-monoalkylated barbituric acids are by the reaction of monoalkyl malonic esters with urea [8], reaction of barbituric acid with aldehydes [9,10] /α,β-unsaturated ketones [11] or by using 5-acylbarbituric acids as synthons [12].

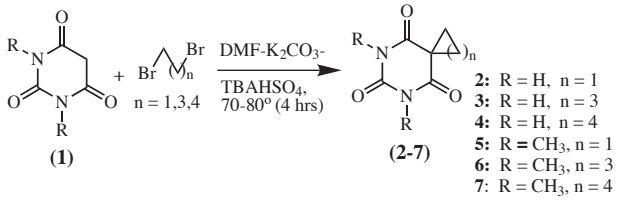
We report herein the synthesis of spiro[2.5], spiro[4.5], spiro[5.5]barbituric acids in a single step by the reaction of N,N'-unsubstituted/-substituted barbituric acids with respective dihalo-alkanes/ arenes under phase transfer catalytic conditions. The reaction mechanism for dialkylation at C_5 has been explained on the basis of tautomeric forms of first alkylated intermediate. Further, C_5-monoalkylated barbituric acids are synthesized by the ring opening of spiro[2.5]barbituric acid with NaCN, PhSH, $HS(CH_2)_2OH$ and Br_2.

Barbituric acid **1** (R=H) on reaction with 1.2 equivalents of dibromoethane in DMF using K_2CO_3 as base (2 equiv) and $TBAHSO_4$ (Tetrabutylammonium hydrogen sulphate) as catalyst (0.01 equiv) gave a solid compound (63%, 50% of the consumed barbituric acid) while 20% barbituric acid was recovered unchanged. The solid compound [M^++1 m/z 155, m.p. 320° (dec), lit. [7] m.p. 320-25°] has been assigned structure **2**. Earlier this compound [7] has been synthesized only in 10% yield where 1,1-cyclopropanedicarboxylic diester was condensed with urea in the presence of a base. In these reported reactions base promoted cyclopropane ring opening before condensation with urea might be the cause of low yield for spiro compound. Similarly, **1** (R=H) on reaction with 1,4-dibromobutane and 1,5-dibromopentane

gave compounds **3** (55%, lit. [7] 53%) and **4** (55%, lit.[4] 33 %) respectively (scheme-1).

Under similar reaction conditions *N*,*N*'-dimethylbarbituric acid (**1**, R=CH_3) on reaction with 1.2 equivalents of dibromoethane gave a white solid (87%, 70% of consumed barbituric acid), m.p. 265-67° and 20% 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/DEPT-135 NMR spectrum, it shows a –ve signal at δ 27.86 (CH_2), a +ve signal at δ 28.96 (CH_3), and quaternary carbon signals at δ 48.76, 150.8 and 171.71 due to C_5, C_2 and C_4/C_6 respectively. ^{1}H and ^{13}C NMR spectra corroborate a symmetrical structure **5** for this compound (scheme 1).

Scheme I

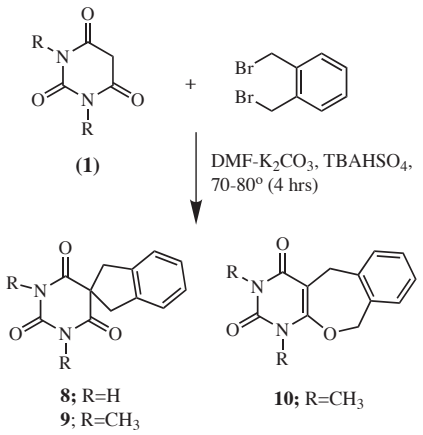


1 (R=CH_3) on reaction with 1,4-dibromobutane and 1,5-dibromopentane gave spiro[4.5] and spiro[5.5]-barbituric acids **6** and **7**. Therefore, the dialkylation with alkyl dihalides at C-5 of barbituric acids provided a straightforward method for synthesizing spirocycloalkyl-barbituric acids in higher yields than the reported ones.

Keeping in mind the role of π-π interactions in the various enzyme-inhibitor complexes, the above synthetic methodology was extended to the reactions of barbituric acids **1** with 1,2-bis[bromomethyl]benzene. **1** (R=H) on reaction with 1,2-bis[bromomethyl]benzene in DMF using K_2CO_3 as base and $TBAHSO_4$ as catalyst provided compound **8** (60%, M^++1 m/z 231). The reaction of **1** (R=CH_3) with 1,2-bis[bromomethyl]benzene gave two compounds. The first one, 60%, M^++1 m/z 259 in ^{1}H NMR spectrum shows a 6H singlet at δ 3.33, a 4H singlet at δ 3.61 and 4H multiplet at δ 7.20-7.26 has been assigned structure **9**. The second compound (20%, M^++1 m/z 258) in ^{1}H NMR spectrum shows two 3H singlets at δ 3.35 and 3.39, two 2H singlets at δ 4.07 and 5.49 along with 4H multiplet at δ 7.33-7.38, has been assigned structure **10** (scheme II).

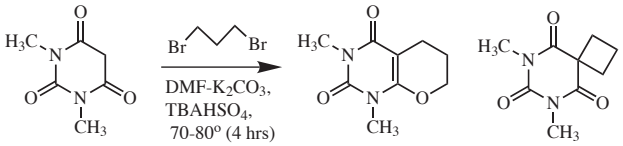
The reactivity behaviour of **1** towards 1,3-dibromopropane is quite different where instead of the formation of spiro compounds, pyranopyrimidines are formed. *N*,*N*'-Dimethylbarbituric acid on reaction with 1,3-dibromopropane gave a solid product (60%), m.p. 122° which in its ^{1}H NMR spectrum shows a 2H quintet at δ 1.98, 2H triplet at δ 2.48, 3H singlet at δ 3.34, 3H singlet at δ 3.35

Scheme II



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 **5**. From this spectral data along with ^{13}C/DEPT-135 NMR spectra, the structure **11** has been assigned to this compound and the expected compound **12** (R=CH_3) was not formed (Scheme III). The non-formation of compound **12** may be attributed to the preferred formation of six membered ring in compound **11** over the four membered ring in **12**.

Scheme III

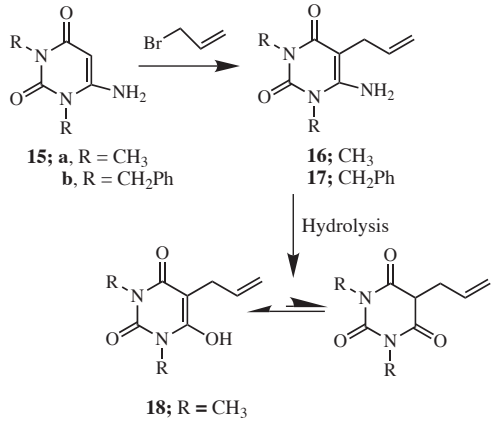


As per the literature reports [13,14], the ^{1}H NMR spectrum of *N*,*N*'-dimethylbarbituric acid shows 2H singlet at δ 3.2 along with a 6H singlet corresponding to two CH_3 groups. The complete absence of olefinic proton at C-5 in the region δ 4-5 indicates the existence of this barbituric acid in triketo- form **1** [15]. Due to the presence of active methylene group at C-5, the first alkylation in barbituric acids takes place at C-5 and not at NH (in case of 1, R=H). The result of first alkylation is intermediate **13**, which could exist in two tautomeric forms **13a** and **13b** (scheme V).

The enolic form of **13** has been confirmed by the synthesis of its analogue 5-allyl-1,3-dimethylbarbituric acid **18** (Scheme IV).

^{1}H NMR spectrum of **18** shows complete absence of C_5-H and its ^{13}C NMR spectrum shows the presence of C_5 as quaternary carbon at δ 75.9.

Scheme IV



15; a, R = CH_3
b, R = CH_2Ph

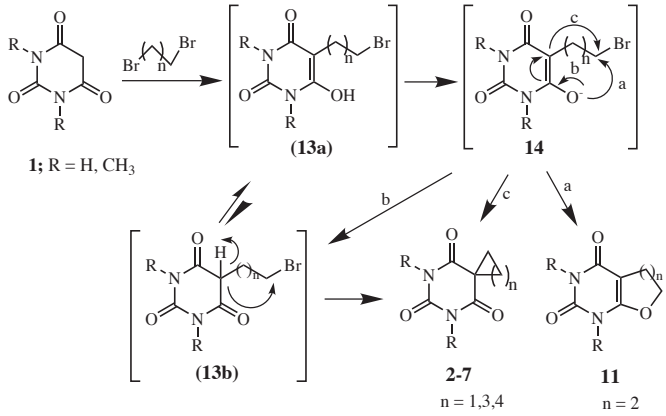
16; CH_3
17; CH_2Ph

18; R = CH_3

The presence of **13** in the enolic form is in favour of the possibility of second alkylation to take place at OH instead of C_5. Moreover, it is controlled by the ease of electron transfer from C_6-O^- towards C-5 and the stabilization of the annulated ring to be formed.

Intermediate **14** (Scheme V) formed by deprotonation of OH, gets transformed to the product through three routes: i) reaction of oxide ion at CH_2-Br *via* **a** forming compound **11**, ii) concerted cyclisation *via* **c** forming compounds **2-7** and iii) formation of keto form **13b** *via* **b**. The stability of 6 membered ring in **11** favours route **a** over **b** and **c** while in other cases for the formation of compounds **2-7**, either route **b** followed by cyclization is adopted or route **c** is followed (Scheme V).

Scheme V



1; R = H, CH_3

(13a)

14

(13b)

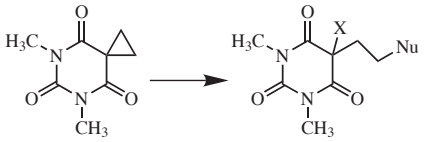
2-7
n = 1,3,4

11
n = 2

Therefore, the existence of C_5-monalkylated barbituric acids in enolic forms creates a competition between C-/O-alkylation and reaction going through the participation of intermediate **14** is predominantly controlled by the stability of the product.

The cyclopropane ring present at C-5 of spirobarbiturates (**2** and **5**) is important because of its reactivity pattern equivalent to carbon-carbon double bond. Compound **5** when taken in ethanol decolorize bromine water and on usual work up gave a thick liquid that has been identified as **19**. The reaction of **5** with thiophenol, NaCN and 2-mercaptoethanol in ethanol gave C_5-monoalkylated products **20** (55%), **21** (52%) and **22** (55%) respectively (Scheme VI).

Scheme VI



5 **19-22**

19; X = Br, Nu = Br
20; X = H, Nu = SPh
21; X = H, Nu = CN
22; X = H, Nu = $S(CH_2)_2OH$

All the new compounds have been characterized by various spectral (^1H NMR, ^{13}C NMR and mass) techniques and elemental analysis. The formation of compounds **20** and **22** 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 compound **11** where the preferred formation of six membered ring over four membered ring leads to the formation of pyranopyrimidine. In spirocyclopropanobar-bituric acid **5** the reactivity of cyclopropane ring helps in the synthesis of C-5 monoalkylated barbituric acids which otherwise are not possible because the C-5 alkylation of barbituric acids is always plagued by dialkylation.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. ^1H 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 δ, ppm). Column chromatography was performed using 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 RSIC, Lucknow.

General Method for Synthesis of Compounds **2-11**.

A mixture of barbituric acid (1.56 g / 1.86 g, 10 mmol), dibromoalkane (2.22 g, 12 mmol), K_2CO_3 (2.76 g, 20 mmol) and $TBAHSO_4$ (catalyst, 0.1 mmol) in DMF was stirred at 70-80° for 4 hrs. On completion of reaction (TLC), it was filtered. After

removing the solvent under reduced pressure, the residue was purified by column chromatography using ethyl acetate and hexane as eluents. Recrystallization from ethanol obtained analytically pure product. The yields are reported with respect to consumed barbituric acid.

5,7-Diaza-spiro[2.5]octane-4,6,8-trione (**2**).

This compound was obtained as whitish solid (ethanol); 63%, mp 320° (dec.); ir (KBr): CO 1670, 1693 cm^{-1}; ^1H nmr ($CDCl_3$+DMSO-d_6): δ 2.26 (s, 4H, 2xCH_2); ^{13}C nmr (normal/DEPT-135): δ 28.2 (-ve, CH_2), 47.8 (C-5), 151.9 (C-2), 171.7 (C-4,C-6); ms: m/z 155 (M^++1).

Anal. Calcd. for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 47.03; H, 4.02; N, 17.92.

7,9-Diaza-spiro[4.5]decane-6,8,10-trione (**3**).

This compound was obtained as whitish solid (ethanol); 55%; mp 259°; ir (KBr): CO 1645, 1660 cm^{-1}; ^1H nmr ($CDCl_3$+DMSO-d_6): δ 1.95 (m, 4H, 2xCH_2), 2.24 (t, 4H, 2xCH_2, J=6.6 Hz); ^{13}C nmr (normal/DEPT-135): δ 28.0 (-ve, CH_2), 39.6 (-ve, CH_2), 57.0 (C-5), 160 (C-2), 174.1 (C-4, C-6); ms: m/z 183 (M^++1).

2,4-Diaza-spiro[5.5]undecane-1,3,5-trione (**4**):

This compound was obtained as whitish solid (ethanol); 55%; mp 279°; ir (KBr): CO 1675, 1692 cm^{-1}; ^1H nmr ($CDCl_3$+DMSO-d_6): δ 1.56-1.65 (m, 2H, CH_2), 1.72-1.83 (m, 4H, 2xCH_2), 1.98 (t, 4H, 2xCH_2, J=6.4 Hz); ^{13}C nmr (normal/DEPT-135): 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); ms: m/z 197 (M^++1).

5,7-Dimethyl-5,7-diaza-spiro[2.5]octane-4,6,8-trione (**5**):

This compound was obtained as whitish solid (ethanol); 87%; mp 265-67°; ir (KBr): CO 1666, 1697 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.23 (s, 4H, 2xCH_2), 3.22 (s, 6H, N-CH_3); ^{13}C nmr (normal/DEPT-135): 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); ms: m/z 183 (M^++1).

Anal. Calcd.. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.44; H, 5.16; N, 15.22.

7,9-Dimethyl-7,9-diaza-spiro[4.5]decane-6,8,10-trione (**6**):

This compound was obtained as whitish solid (ethanol); 52%; mp 87°; ir (KBr): CO 1624 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.93 (t, 4H, 2xCH_2, J=6.6 Hz), 2.22 (t, 4H, 2xCH_2, J=6.6 Hz), 3.31 (s, 6H, N-CH_3); ^{13}C nmr (normal/DEPT-135): δ 27.4 (-ve, CH_2), 28.9 (+ve, N-CH_2), 39.2 (-ve, CH_2), 56.6 (C-5), 151.5 (C-2), 173.4 (C-4, C-6); ms: m/z 212 (M^++1).

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 56.77; H, 6.85; N, 13.19.

2,4-Dimethyl-2,4-diaza-spiro[5.5]undecane-1,3,5-trione (**7**):

This compound was obtained as whitish solid (ethanol); 31%; mp 60°; ir (KBr): CO 1678, 1685 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.51-1.60 (m, 2H, CH_2), 1.67-1.84 (m, 4H, 2xCH_2), 1.96 (t, 4H, 2xCH_2, J=6.4 Hz) 3.30 (s, 6H, N-CH_3); ^{13}C nmr (normal/DEPT-135): 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 225 (M^++1).

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.61; H, 7.37; N, 12.39.

[2.3]Benzo-7,9-diaza-spiro[4.5]decane-6,8,10-trione (**8**):

This compound was obtained as whitish solid (ethanol); 60%; mp 280°; ir (KBr): CO 1684, 1701 cm^{-1}; ^1H nmr ($CDCl_3$+DMSO-d_6): δ 3.73 (s, 4H, 2xCH_2), 7.25-7.36 (m, 4H, Ph); ^{13}C nmr (normal/DEPT-135): 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); ms: m/z 231 (M^++1).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.40; H, 4.62; N, 11.92.

[2.3]Benzo-7,9-dimethyl-7,9-diaza-spiro[4.5]decane-6,8,10-trione (**9**).

This compound was obtained as whitish solid (ethanol); 60%; mp 120°; ir (KBr): CO 1678 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.33 (s, 6H, N-CH_3), 3.61 (s, 4H, 2xCH_2), 7.20-7.26 (m, 4H, Ph); ^{13}C nmr (normal/DEPT-135): 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); ms: m/z 259 (M^++1).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.08; H, 5.78; N, 10.83.

1,3-Dimethyl-5,10-dihydro-1*H*-11-oxa-1,3-diaza-dibenzo[*a*,*b*]-cycloheptene-2,4-dione (**10**).

This compound was obtained as whitish solid (ethanol); 20%; mp 105°; ir (KBr): CO 1681 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.35 (s, 3H, N-CH_3), 3.39 (s, 3H, N-CH_3), 4.07 (s, 2H, CH_2), 5.49 (s, 2H, O-CH_2), 7.33-7.38 (m, 4H, Ph); ^{13}C nmr (normal/DEPT-135): 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); ms: m/z 258 (M^++1).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.38; H, 5.78; N, 11.10.

1,3-Dimethyl-1*H*,5*H*-6,7-dihydro-pyrano[2,3-*d*]pyrimidine-2,4-dione (**11**).

This compound was obtained as whitish solid (ethanol); 60%; mp 122°; ir (KBr): CO 1610, 1631 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.92-2.04 (m, 2H, CH_2), 2.48 (t, 2H, CH_2, J=6.4 Hz), 3.34 (s, 3H, N-CH_3), 3.36 (s, 3H, N-CH_3), 4.35 (t, 2H, O-CH_2, J=5.2 Hz); ^{13}C nmr (normal/DEPT-135): 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); ms: m/z 197 (M^++1).

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.29; H, 5.82; N, 14.10.

Synthesis of Compounds **16** and **17**.

Equimolar amounts of 1,3-dialkyl-6-aminouracil (1.55g, 10 mmol) and allyl bromide (1.20 g, 10 mmol) were stirred at 70-80° in DMF (10 ml) using K_2CO_3 (2.76 g, 20 mmol) as base and $TBAHSO_4$ as catalyst (0.1 mmol) for 3 hrs. After filtration, solvent was removed under reduced pressure. The impure residue was purified by column chromatography using ethyl acetate hexane as eluents and recrystallized from ethanol.

5-Allyl-6-amino-1,3-dimethyl-1*H*-pyrimidine-2,4-dione (**16**).

This compound was obtained as whitish solid (ethanol); 53%; mp 165°; ^1H nmr ($CDCl_3$): δ 3.28 (dd, 2H, CH_2, J=8.0 Hz, J=10.0 Hz), 3.38 (s, 3H, N-CH_3), 3.49 (s, 3H, N-CH_3), 4.49 (bs,

2H, NH_2), 5.16 (dd, 2H, CH_2, J=6.0 Hz, J=8.0 Hz), 5.65 (m, 1H, CH); ^{13}C nmr (normal/DEPT-135): δ 28.1 (-ve, CH_2), 28.2 (+ve, CH_3), 29.3 (+ve, CH_3), 85.0 (C-5), 115.3 (-ve, CH_2), 135.4 (+ve, CH), 151.2 (C-2), 151.4 (C-4), 162.4 (C-6); ms: m/z 196 (M^+).

5-Allyl-6-amino-1,3-dibenzyl-*1H*-pyrimidine-2,4-dione (**17**).

This compound was obtained as yellowish oil; 42%; ^1H nmr ($CDCl_3$): δ 2.41 (dd, 2H, CH_2, J=6.0 Hz, J=8.0 Hz), 2.72 (dd, 2H, CH_2, J=6.0 Hz, J=8.0 Hz), 4.94 (dd, 2H, CH_2, J=4.0 Hz, J=10.0 Hz), 5.01 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 5.34 (m, 1H, CH); 7.28 (m, 10H, 2xPh); ^{13}C nmr (normal/DEPT-135): δ 44.1 (-ve, CH_2), 45.0 (-ve, CH_2), 46.0 (-ve, CH_2), 54.3 (C-5), 120.7 (-ve, CH_2), 125.9 (+ve, ArCH), 127.3 (+ve, ArCH), 127.5 (+ve, ArCH), 128.3 (+ve, ArCH), 128.6 (+ve, ArCH), 128.8 (ArC), 128.9 (+ve, ArCH), 130.3 (+ve, CH), 136.6 (ArC), 150.5 (C-2), 161.5 (C-4), 170.2 (C-6).

Syntheses of **18**.

Method A: 5-Allyl-6-amino-1,3-dimethyluracil (1.95 g, 10 mmol) and *m*-chloroperbenzoic acid (1.725 g, 10 mmol) were taken in $CHCl_3$ (10 ml) and stirred for 12 hrs at room temperature. The reaction was monitored by TLC. After the starting material is consumed, the reaction mixture was treated with saturated solution of $NaHCO_3$ and extracted with $CHCl_3$. The combined organic extractions were dried over anhydrous sodium sulphate. On removing the solvent, the crude residue was purified by column chromatography using ethyl acetate and hexane as eluents.

Method B: 5-Allyl-6-amino-1,3-dimethyluracil (1.95 g, 10 mmol) and oxone (12.30 g, 20 mmol) were stirred at 0° in Acetone-Water mixture (7:3) for 2 hrs. The reaction was monitored by TLC and after the completion of the reaction, it was extracted with $CHCl_3$. The impure residue obtained after the removal of solvent was purified by column chromatography with ethyl acetate-hexane mixture.

5-Allyl-6-hydroxy-1,3-dimethyl-*1H*-pyrimidine-2,4-dione (**18**)**:**

This compound was obtained as yellowish oil; 45%; ^1H nmr ($CDCl_3$): δ 2.70 (d, 2H, CH_2, J=6 Hz), 3.31 (s, 6H, N-CH_3), 5.21 (dd, 2H, CH_2, J=6.0 Hz, J=8.0 Hz), 5.61 (m, 1H, CH); ^{13}C nmr (normal/DEPT-135): δ 28.8 (+ve, CH_3), 46.9 (-ve, CH_2), 75.9 (C-5), 122.0 (-ve, CH_2), 128.4 (+ve, CH), 150.5 (C-2), 169.8 (C-4, C-6); ms: m/z 197 (M^+).

General Method for Synthesis of Compounds **19-22**.

A mixture of **5** (1.82 g, 10 mmol) and the appropriate reagent *viz*. Br_2, PhSH, NaCN, $HS(CH_2)_2OH$ (10 mmol) was taken in ethanol and stirred at 50-60° for 8-10 hrs. After removing the solvent, the impure residue was purified by column chromatography using ethyl acetate-hexane as eluents.

5-Bromo-5-(2-bromoethyl)-1,3-dimethyl-pyrimidine-2,4,6-trione (**19**):

This compound was obtained as yellowish oil; 60%; ir (KBr): CO 1666, 1697 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.20 (t, 2H, CH_2, J=8.0 Hz), 3.40 (s, 6H, N-CH_3), 3.45 (t, 2H, CH_2, J=8.0 Hz); ^{13}C nmr (normal/DEPT-135): 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 (C-5), 149 (C-2), 165.5 (C-4), 168.7 (C-6); ms: m/z 343 (M^++1).

Anal. Calcd. for $C_8H_{10}Br_2N_2O_3$: C, 28.10; H, 2.95; N, 8.19. Found: C, 28.25; H, 3.01; N, 8.11.

1,3-Dimethyl-5-(2-phenylsulfanyl-ethyl)-1*H*-pyrimidine-2,4,6-trione (**20**).

This compound was obtained as white solid (ethanol); 55%; mp 175°; ir (KBr): CO 1645 cm^{-1}; ^1H nmr ($CDCl_3$): δ 3.24 (s, 3H, N-CH_3), 3.29 (s, 3H, N-CH_3), 3.30 (t, 2H, CH_2, J=6.3 Hz), 4.16 (t, 2H, S-CH_2, J=5.8 Hz), 5.01 (s, 1H, C-5H), 7.27-7.39 (m, 5H, Ph); ^{13}C nmr (normal/DEPT-135): 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 293 (M^++1).

Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; S, 10.97. Found: C, 57.29; H, 5.32; N, 9.28; S, 10.82.

3-(1,3-Dimethyl-2,4,6-trioxo-hexahydro-pyrimidin-5-yl)-propionitrile (**21**).

This compound was obtained as yellowish oil; 52%; ir (KBr): CO 1660, CN 2250 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.28 (t, 2H, CH_2, J=6.0 Hz), 3.33 (s, 3H, N-CH_3), 3.37 (s, 3H, N-CH_3), 3.42 (t, 2H, CH_2, J=6.4 Hz,), 5.11 (s, 1H, C-5H), ^{13}C nmr (normal/DEPT-135): 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 210 (M^++1).

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.82; H, 5.39; N, 19.95.

5-[2-(2-Hydroxy-ethylsulfanyl)-ethyl]-1,3-dimethyl-pyrimidine-2,4,6-trione (**22**).

This compound was obtained as yellowish oil; 55%; ir (KBr): CO 1680 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.87 (t, 2H, CH_2, J=4.8 Hz), 3.31 (s, 3H, N-CH_3), 3.40 (s, 3H, N-CH_3), 3.68 (t, 2H, CH_2, J=4.8 Hz), 3.91 (t, 2H, S-CH_2, J=5.4 Hz), 4.34 (t, 2H, CH_2, J=5.4 Hz), 5.11 (s, 1H, C-5H); ^{13}C nmr (normal/DEPT-135): δ 24.6 (-ve, CH_2), 27.3 (+ve, N-CH_3), 28.9 (+ve, N-CH_3), 41.5 (-ve, S-CH_2), 60.2 (-ve, S-CH_2), 69.3 (-ve, O-CH_2), 78.3 (+ve, C-5H), 169.8 (C-2), 163.2 (C-4,C-6); ms: m/z 261 (M^++1).

Anal. Calcd. for $C_{10}H_{16}N_2O_4S$: C, 46.14; H, 6.20; N, 10.76, S, 12.32. Found: C, 46.20; H, 6.35; N, 10.58, S, 12.20.

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