A Facile One-pot Synthesis of Novel Substituted 1,2,3,4-Tetrahydropyrimidines Part 5 [1]: Synthesis of Bis[(1-alkyl/aralkyl)-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl]alkane and Benzene, Bis[3-phenyl-7-methyl-4,5,6,7-tetrahydropyrazolo[3,4-*d*]-pyrimidinyl]alkane and Bis[1-benzyl-7-phenyl-1,2,3,4-tetrahydro-pyrazolo[1,5-*a*]triazinyl]alkane and Benzene

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Bis-1,2,3,4-tetrahydropyrimidinylalkanes/benzenes **2a-f** have been synthesized by the reaction of N,S-acetals with formaldehyde and diamines. Reaction of pyrazoles **3a** and **3b** with diamines and formaldehyde yield bis-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidinylalkanes **4a-b** and bis-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazinylalkanes and benzene **5a-c** respectively in good yields.

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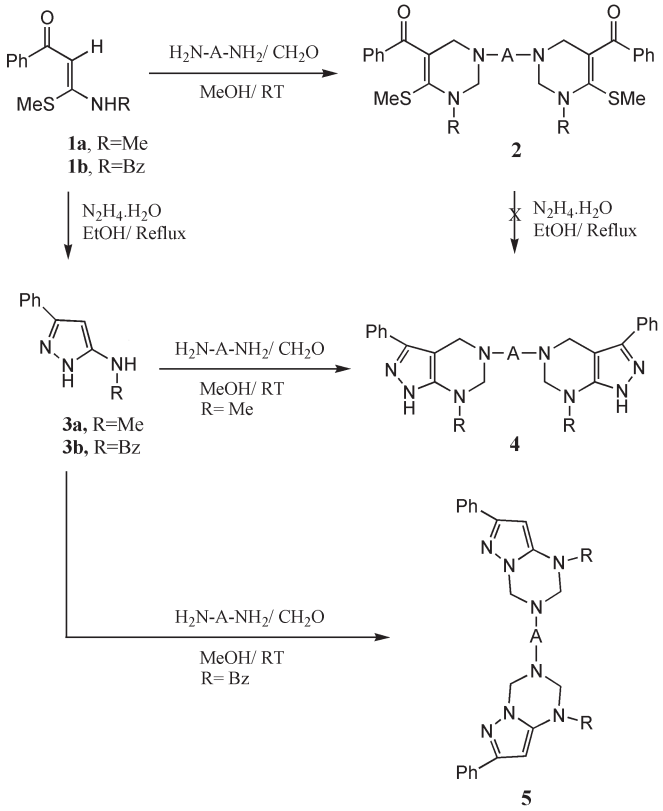
Several pyrazolo[3,4-*d*]pyrimidines and their mercapto analogues are known to possess important biological properties [2-6]. In view of this, we reported the synthesis of 4,5,6,7-tetrahydro derivatives [7]. However, to the best of our knowledge, bis-pyrazolotetrahydropyrimidines are unknown in the literature and hence their biological properties remain unexplored. Prompted by the above observations and in continuation with our on-going program on the development of novel synthetic strategies for tetrahydropyrimidines [1, 8-10], we undertook the present investigation and the results of our studies are reported herein.

Thus, when a mixture of N,S-acetal **1a** [11], ethylenediamine and formaldehyde (2:1:4) in methanol was stirred at room temperature, work up of the reaction mixture yielded an off white solid in 72% yield, which was characterized as 1,2-bis(1-methyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl)ethane (**2a**). The reaction was found to be general with other diamines and with corresponding **1** to give the respective **2b-f** in 52-72% overall yields. The structures of these products were confirmed on the basis of analytical and spectral data. Thus, the ir spectra of **2a-f** showed strong absorption bands in the range 1603-1639 cm^{-1} due to carbonyl group stretching frequencies. The ^1H nmr spectra showed singlets due to methylene protons at C_2 and C_4 of the tetrahydropyrimidine ring in the range of δ 3.80-4.55 and δ 3.40-4.12 respectively. The singlets due to NMe protons in **2a-c** appeared in the range of δ 3.00-3.10 while the benzylic methylene protons in **2d-f** gave singlets in the range of δ 3.65-4.30. In the spectra of **2a** and **2d**, the signals due to the protons of ethylene chain appeared as singlets at 2.80 and 2.56 ppm respectively, whereas the NCH_2 protons of butylene chain in compounds **2b** and **2e** gave multiplets in the range of δ 2.35-2.52. The signals corresponding to the methylene protons at C_2 and C_3 of the butylene chain of **2b** and **2e** are observed as multiplets resonating between δ 1.40-1.62 ppm. The singlets due to protons of methylthio group appeared between δ 1.90-1.98, while the aromatic protons gave multiplets in the usual range.

Further reaction of **2** with hydrazine hydrate to achieve the synthesis of **4** resulted in the formation of a complex reaction mixture from which isolation of the desired product was unsuccessful. This is probably due to the cleavage of the tetrahydropyrimidine ring in the presence of this nucleophilic reagent under experimental conditions. We then turned our attention to another strategy involving the conversion of **1** into pyrazole **3** [12] and then **3** into the desired bis-pyrazolotetrahydropyrimidines **4** (Scheme).

Thus, when a mixture of 3(5)-methylaminopyrazole **3a**, ethylenediamine and formaldehyde (2:1:4) was stirred at room temperature in methanol for 5 hours, work up of the reaction mixture yielded **4a** in 53% yields, the structure of which was proposed to be 1,2-bis(3-phenyl-7-methyl-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidinyl)ethane on the basis of analytical and spectral data. Similarly, **3a** reacted with butylenediamine and formaldehyde under identical conditions to give **4b** in 55% yield. However, the reaction of **3a** with *p*-phenylenediamine and formaldehyde gave an intractable reaction mixture from which no product could be isolated. Interestingly, when 3(5)-benzylaminopyrazole **3b** was reacted with ethylenediamine and formaldehyde under identical conditions, the product isolated (51%) was characterized as 1,2-bis(1-benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazinyl)ethane (**5a**) instead of the corresponding bis-pyrazolopyrimidinylethane. The reaction of **3b** was found to follow a similar course of reaction with other diamines giving **5b** and **5c** in 50 and 55% yields respectively. The bis-pyrazolotriazinyl derivatives **5** were distinguished from the corresponding bis-pyrazolopyrimidinyl derivatives by the

Scheme



Compd	R	A
2a, 4a	Me	-$(CH_2)_2$-
2b, 4b	Me	-$(CH_2)_4$-
2c	Me	
2d, 5a	Bz	-$(CH_2)_2$-
2e, 5b	Bz	-$(CH_2)_4$-
2f, 5c	Bz	

presence of a signal due to H-8 between δ 5.72-6.05 (2 s, 2x1H) in their ^{1}H nmr spectra. In addition, the band due to NH in the ir spectra of **4a-b** was found absent in those of **5a-c**. The difference in the reactivities of 3(5)-methylaminopyrazole **3a** and the corresponding benzylaminopyrazole **3b** to give **4** and **5** respectively could be explained in terms of decreased nucleophilicity of C_4 position in **3b** because of reduced delocalization of the lone pair of electrons of the benzylamino nitrogen due to hyperconjugation of CH_2 of benzyl group, while the nitrogen lone pair in methylamino group of **3a** is completely delocalized over pyrazole ring, thus facilitating ring closure through C_4 position.

The present investigation describes facile syntheses of hitherto unreported bis-tetrahydropyrimidines, bis-pyrazolotetrahydropyrimidines and bis-pyrazolotetrahydrotriazines.

EXPERIMENTAL

Melting points were recorded by open capillary method and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 983 spectrometer. ^{1}H nmr (90 MHz) spectra were recorded on Varian EM-390 spectrometer. High-resolution ^{1}H nmr and ^{13}C nmr (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard fashion with reference to TMS as internal reference. FAB-mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 Mass spectrometer using Argon as the FAB gas and m-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Vario-EL III instrument.

Bis[(1-Alkyl/aralkyl)-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl]alkanes/benzenes (**2a-f**).

General Procedure.

A mixture of diamine (1 mmol) and formaldehyde (4 mmol, 40% solution) in 2 ml methanol was stirred at room temperature

for 10 minutes. To this was added a solution of enaminone **1** (2 mmol) in 5-6 ml methanol and the resulting mixture stirred for 3-8 hours in case of **2b**, **2c**, **2e**, **2f** and 22-30 hours in case of **2a** and **2d**. After completion of the reaction (monitored by tlc), the reaction mixture was cooled in ice water and the precipitated product was collected by filtration, washed with cold methanol (3 x 1 ml) and dried to give pure **2a-2f**, which were recrystallized from methanol.

1,2-Bis (1-methyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl)ethane (**2a**).

The compound was obtained as a white solid in 72% yield, mp 159-160° C; ir (KBr): 1455, 1554, 1625 cm-^{1}; ^{1}H nmr ($CDCl_3$): δ 1.98 (s, 6H, 2 CH_3), 2.80 (s, 4H, 2 CH_2), 3.10 (s, 6H, 2 CH_3), 3.58 (s, 4H, 2 CH_2), 3.98 (s, 4H, 2 CH_2), 7.35-7.48 (m, 6H), 7.68-7.72 (m, 4H); ^{13}C nmr ($CDCl_3$): δ 16.61, 40.04, 52.16, 53.74, 72.94, 115.28, 127.76, 128.33, 130.66, 142.04, 152.71, 195.73; ms: m/z 523 (MH^+).

Anal. Calcd. for $C_{28}H_{34}N_4O_2S_2$ (522.73): C, 64.34; H, 6.56; N, 10.72. Found: C, 64.11; H, 6.51; N, 10.79.

1,4-Bis (1-Methyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl)butane (**2b**).

The compound was obtained as a white solid in 66% yield, mp 116-118 °C; ir (KBr): 1542, 1603 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.58-1.62 (m, 4H), 1.90 (m, 6H, 2 CH_3), 2.42-2.52 (m, 4H), 3.05 (s, 6H, 2 CH_3), 3.45 (s, 4H, 2 CH_2), 3.80 (s, 4H, 2 CH_2), 7.28-7.40 (m, 6H), 7.59-7.64 (m, 4H); ^{13}C nmr ($CDCl_3$): δ 16.47, 25.49, 40.09, 53.65, 53.86, 72.50, 115.83, 127.75, 128.35, 130.66, 142.02, 152.71, 195.82; ms: m/z 551 (MH^+).

Anal. Calcd. for $C_{30}H_{38}N_4O_2S_2$ (550.78): C, 65.42; H, 6.95; N, 10.17. Found: C, 65.63; H, 6.89; N, 10.22.

1,4-Bis (1-Methyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl)benzene (**2c**).

The compound was obtained as a white solid in 56% yield, mp 210-211 °C; ir (KBr): 1510, 1555, 1625 cm-^{1}; ^{1}H nmr ($CDCl_3$): δ 1.90 (s, 6H, 2 CH_3), 3.00 (s, 6H, 2 CH_3), 4.12 (s, 4H, 2 CH_2), 4.45 (s, 4H, 2 CH_2), 7.19-7.29 (m, 3H), 7.30-7.43 (m, 7H), 7.65-7.70 (m, 4H); ms: m/z 571 (MH^+).

Anal. Calcd. for $C_{32}H_{34}N_4O_2S_2$ (570.77): C, 67.34; H, 6.00; N, 9.82. Found: C, 67.08; H, 6.04; N, 9.76.

1,2-Bis (1-Benzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl)ethane (**2d**).

The compound was obtained as a white solid in 52% yield, mp 101-102 °C; ir (KBr): 1522, 1634 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.90 (s, 6H, 2 CH_3), 2.56 (s, 4H, 2 CH_2), 3.45 (s, 4H, 2 CH_2), 3.75 (s, 4H, 2 CH_2), 4.55 (s, 4H, 2 CH_2), 7.22-7.45 (m, 16H), 7.68-7.72 (m, 4H); ^{13}C nmr ($CDCl_3$): δ 16.79, 52.14, 54.48, 55.12, 69.57, 117.36, 127.37, 127.66, 127.89, 128.52, 128.76, 131.08, 141.41, 151.64, 195.84; ms: m/z 675 (MH^+).

Anal. Calcd. for $C_{40}H_{42}N_4O_2S_2$ (674.92): C, 71.18; H, 6.27; N, 8.30. Found: C, 71.42; H, 6.22; N, 8.36.

1,4-Bis (1-Benzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl)butane (**2e**).

The compound was obtained as a white solid in 60% yield, mp 149-159 °C; ir (KBr): 1562, 1639 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.40-1.50 (m, 4H, 2 CH_2), 1.90 (s, 6H, 2 CH_3), 2.35-2.40 (m, 4H, 2 CH_2), 3.40 (s, 4H, 2 CH_2), 3.65 (s, 4H, 2 CH_2), 4.55 (s, 4H, 2 CH_2) 7.25-7.41 (m, 16H), 7.69-7.72 (m, 4H); ^{13}C nmr ($CDCl_3$): δ 16.66, 25.21, 53.89, 54.32, 55.19, 69.46, 117.86, 127.69, 127.87, 128.51, 128.70, 131.05, 138.13, 141.42, 151.60, 195.96; ms: m/z 703 (MH^+).

Anal. Calcd. for $C_{42}H_{46}N_4O_2S_2$ (702.97): C, 71.76; H, 6.60; N, 7.97. Found: C, 72.02; H, 6.64; N, 8.04.

1,4-Bis (1-Benzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl)benzene (**2f**).

The compound was obtained as a white solid in 70% yield, mp 197-198 °C; ir (KBr): 1516, 1568, 1629 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.95 (s, 6H, 2 CH_3), 4.00 (s, 4H, 2 CH_2), 4.30 (s, 4H, 2 CH_2), 4.52 (s, 4H, 2 CH_2), 7.28-7.45 (m, 20H), 7.75-7.79 (m, 4H); ^{13}C nmr ($CDCl_3$): δ 16.37, 50.49, 54.91, 67.00, 117.40, 126.94, 127.54, 127.97, 128.29, 128.59, 128.83, 131.37, 137.71, 140.92, 141.94, 152.63, 195.84; ms: m/z 723 (MH^+).

Anal. Calcd. for $C_{44}H_{42}N_4O_2S_2$ (722.96): C, 73.10; H, 5.86; N, 7.75. Found: C, 73.31; H, 5.90; N, 7.69.

Bis (3-Phenyl-7-methyl-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidinyl)alkanes (**4a-b**).

General Procedure.

A mixture of diamine (1 mmol) and formaldehyde (4 mmol, 40% solution) in 2 ml methanol was stirred at room temperature for 10 minutes. To this was added a solution of aminopyrazole **3a** (2 mmol) in 5-6 ml methanol and the resulting mixture stirred for 3-8 hours. After the completion of the reaction (monitored by tlc), the solvent was distilled off, the residue dissolved in chloroform (5 ml), the solution washed with water (3 x 3 ml), dried over anhydrous Na_2SO_4 and the solvent evaporated to give crude bis-pyrazolotetrahydropyrimidines **4a-b**, which were purified by passing through neutral alumina column using ethylacetate as eluant.

1,2-Bis (3-Phenyl-7-methyl-4,5,6,7-tetrahydropyrazolo[3,4-*d*]-pyrimidinyl)ethane (**4a**).

This compound was obtained as a white solid in 53% yield, mp 248-250 °C: ir (KBr): 1445, 3170 cm^{-1}; ^{1}H nmr($CDCl_3$): δ 2.50 (s, 4H, 2 CH_2), 2.73 (s, 6H, 2 CH_3), 3.75 (s, 4H, 2 CH_2), 3.90 (s, 4H, 2 CH_2), 7.25-7.65 (m, 10H), 12.05 (broad multiplet 2H, 2 NH): ^{13}C nmr ($CDCl_3$): δ 36.79, 49.34, 52.11, 71.69, 98.65, 125.35, 126.40, 127.45, 128.81, 129.90; ms: m/z 455 (MH^+).

Anal. Calcd. for $C_{26}H_{30}N_8$ (454.57): C, 68.70; H, 6.65; N, 24.65. Found: C, 68.95; H, 6.70; N, 24.53.

1,4-Bis (3-Phenyl-7-methyl-4,5,6,7-tetrahydropyrazolo[3,4-*d*]-pyrimidinyl)butane (**4b**).

This compound was obtained as a white solid in 55% yield, mp 214-216 °C ir (KBr): 1363, 3416 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.41-1.55 (m, 4H, 2 CH_2), 2.41-2.55 (m, 4H, 2 CH_2), 2.73 (s, 6H, 2 CH_3), 3.65 (s, 4H, 2 CH_2), 3.85 (s, 4H, 2 CH_2), 7.25-7.55 (m, 10H), 12.00 (broad multiplet, 2H, 2 NH); ms: m/z 483 (MH^+).

Anal. Calcd. for $C_{28}H_{34}N_8$ (482.62): C, 69.68; H, 7.10; N, 23.22. Found: C, 69.42; H, 7.16; N, 23.33.

Bis(1-Benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazinyl)alkanes/benzene (**5a-c**).

General Procedure.

A mixture of diamine (1 mmol) and formaldehyde (4 mmol, 40% solution) in 2 ml methanol was stirred at room temperature for 10 minutes. To this was added a solution of aminopyrazole **3b**

(2 mmol) in 5-6 ml methanol and the resulting mixture stirred for 3-8 hours. After the completion of the reaction (monitored by tlc), the reaction mixture was cooled in ice water and the precipitated product was collected by filtration, washed with cold methanol (3 x1 ml) and dried to give pure **5a-c**, which were recrystallized from methanol.

1,2-Bis (1-Benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]-triazinyl)ethane (**5a**).

This compound was obtained as a white solid in 51% yield, mp 225-226 °C; ir (KBr): 1399, 1634 cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.90 (s, 4H, 2 CH_2), 3.98 (s, 4H, 2 CH_2), 4.25 (s, 4H, 2 CH_2), 4.99(s, 4H, 2 CH_2), 5.72 (s, 2H, 2 C_8-H), 7.24-7.37 (m, 16H), 7.70-7.73 (m, 4H); ms: m/z 607 (MH^+).

Anal. Calcd. for $C_{38}H_{38}N_8$ (606.76): C, 75.22; H, 6.31; N, 18.47. Found: C, 75.48; H, 6.26; N, 18.56.

1,4-Bis (1-Benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]-triazinyl)butane (**5b**).

This compound was obtained as white solid in 50% yield, mp 132-133 °C; ir (KBr): 1576, 1637 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.35-1.45 (m, 4H, 2 CH_2), 2.69-2.82 (m, 4H, 2 CH_2), 4.05 (s, 4H, 2 CH_2), 4.33 (s, 4H, 2 CH_2), 5.03 (s, 4H, 2 CH_2), 5.75 (s, 2H, 2 C_8-H), 7.23-7.45 (m, 16H), 7.70-7.80 (m, 4H); ms: m/z 635 (MH^+).

Anal. Calcd. for $C_{40}H_{42}N_8$ (634.82): C, 75.68; H, 6.67; N, 17.65. Found: C, 75.40; H, 6.73; N, 17.54.

1,4-Bis (1-Benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]-triazinyl)benzene (**5c**).

This compound was obtained as white solid in 55% yield, mp 154-156 °C ir (KBr): 1454, 1515, 1576 cm^{-1}; ^1H nmr ($CDCl_3$): δ 4.59 (s, 4H, 2 CH_2), 4.83 (s, 4H, 2 CH_2), 5.85 (s, 4H, 2 CH_2), 6.05 (s, 2H, 2 C_8-H), 7.45–7.80 (m, 21H), 8.09-8.12 (m, 3H); ^{13}C nmr ($CDCl_3$): δ 53.93, 65.06, 65.67, 83.75, 120.59, 125.40, 127.55, 128.47, 128.64, 133.71, 136.45, 143.21, 148.49, 150.49; ms: m/z: 655 (MH^+).

Anal. Calcd. for $C_{42}H_{38}N_8$ (654.81): C, 77.04; H, 5.85; N, 17.11. Found: C, 77.30; H, 5.80; N, 17.21.

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