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A Convenient Synthesis of 5-Deaza Nonclassical Antifolates: Reaction of Cyanothioacetamide With Sodium Salts of 2-(Hydroxymethylene)-1-cycloalkanones

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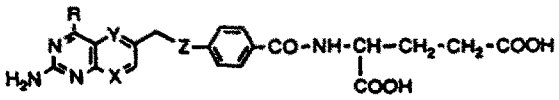
Abstract: Condensation of cyanothioacetamide with sodium salts of 2-(Hydroxymethylene)-1-cycloalkanones afforded the corresponding pyridine-2(1H)-thiones **4**. Compounds **4** served as a key intermediates for the synthesis of condensed 2,4-diaminopyrido[2,3-d]pyridines **7**. Compounds **7** were of interest as potential inhibitors of dihydrofolate reductase.

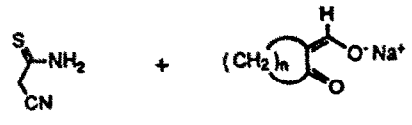
The 5-deaza analogue **1a** of aminopterin was recently synthesized and reported to be significantly active, both in vitro and in vivo.[1, 2] Stone et al have reported that 5-deazafolic acid **1b** is a potent inhibitor of dihydrofolate reductase. The 5-deaza-5-methylpteridin derivative[3] has exhibited cytotoxicity againest various experimental tumors as potently as methotrexate **1c**,[4, 5] one of the most effective antimetabolites currently used in the treatment of various solid tumors.[6, 7] A disadvantage of classical folates is that they require a transport mechanism into the cell. Cells which lack this transport mechanism are not susceptible to the action of classical antifolates. As a consequence some nonclassical antifolates which lack the L-glutamate portion have been developed.[8] These nonclassical analogues are highly lipophilic and are transported into cells by passive diffusion and have a broad range of activity. As a part of our program directed for development of new simple and efficient procedures for the synthesis of antimetabolites,[9-11] we have recently reported different successful approaches for synthesis of purine, pyrimidine and 5-deazafolic acid analogues.[12-14] Derivatives of these ring systems are interesting because they have useful properties as antimetabolites in biochemical reactions. The present paper deals with a novel synthesis of condensed pyridine-2(1H)-thiones and condensed pyrido[2,3-d]pyridines. Moreover, the results of our work aimed to define the scope and limitation of our procedures for the synthesis of pyridine and their important condensed derivatives are also reported.

Thus it has been found that cyanothioacetamide **2** reacted with sodium salts of 2-(hydroxymethylene)-1-cycloalkanones **3** to give the condensed 3-cyano-pyridine-2(1H)-thione derivatives **4**. The structures of **4**(a-e) were established on the basis of their elemental analysis and spectral data. Thus, structure **4b** is supported by its mass spectrum which showed a molecular formula $C_{10}H_{10}N_2S$ (M^+ 190). ^1H NMR spectroscopy was used to confirm this

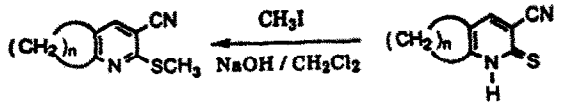


1

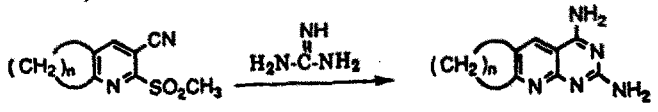
a, R = NH_2, X = N, Y = CH, Z = NH
b, R = OH, X = N, Y = CH, Z = NH
c, R = NH_2, X = N, Y = N, Z = NCH_3



2 **3**



5 **4**



6 **7**

3, 4, 5, 6, 7 a, n = 3
b, n = 4
c, n = 5
d, n = 6
e, n = 8

structure for the product. Thus, ^{1}H NMR revealed a singlet at δ 7.83 ppm assigned for pyridine 4-H proton and a broad band at δ 13.86 ppm assigned to the NH proton . Compounds **4** bearing latent functional substituent were found useful for the synthesis of fused pyridines. Thus, compounds **4** reacted with methyl iodide in methylene choride-sodium hydroxide to afford the corresponding S-methyl derivatives **5**. The ^{1}H NMR spectrum for **5b** showed a band at δ 2.65 ppm assigned to SCH_3 group. The mass spectrum showed a molecular formula $C_{11}H_{12}N_2S$ (M^+ 204). When compounds **5** were subjected to oxidation with m-chloroperbenzoic acid in ethanol at room temperature, the corresponding sulfone derivatives **6** were obtained. The structure of compounds **6** was established on the basis of elemental analysis and spectral data. Thus, the ^{1}H NMR spectrum showed a band at δ 3.43 ppm assigned to the SO_2CH_3 group. Direct treatment of **6** with guanidine afforded the 5-deazapteridin derivatives **7**. The structure of compounds **7** was established on the basis of their elemental analysis and spectral data. The IR spectrum of compound **7b** showed the absence of a CN band and its ^{1}H NMR spectrum showed two broad singlets at δ 6.32, 7.16 ppm assignable to two amino groups. The mass spectrum was compatible with the molecular formula $C_{11}H_{13}N_5$ (M^+ 215).

In summary, we have achieved a regiospecific synthesis of interesting pyridine-2(1H)-thiones and 2,4-diaminopyrido[2,3-d]pyridines by the reaction of cyanothioacetamide with sodium salts of 2-(hydroxymethylene)-1-cycloalkanones. The obtained 5-deaza analogues of aminopterin are now under biological evaluation studies.

EXPERIMENTAL

All melting points are uncorrected. IR were obtained (KBr disc) on a Pye unicam Spectra-1000 or on a Shimadzu IR 200 instrument. ^{1}H NMR spectra wre mearured on a Wilmad 270 MHz spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Centre at Cairo University.

Cycloalkane ring-fused 3-cyanopyridine-2(1H)-thiones 4a-e

A solution of 2-(hydroxymethylene)-1-cycloalkanones **3** (0.01 mol), 2-cyanothioacetamide (0.01 mol), and piperidine acetate (9.5 ml) [prepared from glacial acetic acid (4.2 ml), water (10ml) and piperidine (7.2 ml)]in water (50 ml) was refluxed for 10 minutes. Acetic acid (15 ml) was added to the hot solution. The precipitated solid was collected by filtration and crystallized from the appropriate solvent.

4a: Yield (85%); m.p. 190°C; IR (KBr) υ 3450, 3400 (NH), 2222 (CN); ^{1}H NMR (DMSO) δ 1.91 (m, 2H, CH_2), 2.61-2.95 (m, 4H, $2CH_2$), 7.95 (s, 1H, pyridine H-4), 14.33 (s, br, 1H, NH); MS, m/e 176; (Calcd for $C_9H_8N_2S$: C, 61.4; H, 4.5; N, 15.9. Found: C, 61.0; H, 4.4; N, 15.7%).

4b: Yield (80%); m.p. 250-252°C; IR (KBr) υ 3520, 3440 (NH), 2220 (CN); ^{1}H NMR (DMSO) δ 1.55-1.81 (m, 6H, $3CH_2$), 2.52-2.81 (m, 2H, CH_2), 7.83 (s, 1H, pyridine H-4), 13.86 (s, br, 1H, NH); MS, m/e 190; (Calcd for $C_{10}H_{10}N_2S$: C, 63.2; H, 5.3; N, 14.7. Found: C, 63.0; H, 5.5; N, 14.5%).

4c: Yield (70%); m.p. 247°C; IR (KBr) υ 2430 (NH), 2230 (CN); ^{1}H NMR (DMSO) δ 1.41-1.88 (m, 6H, $3CH_2$), 2.38-2.72 (m, 2H, CH_2), 2.82-3.00 (m, 2H, CH_2), 7.95 (s, 1H, pyridine H-4), 13.96 (s, br, 1H, NH); MS, m/e 204; (Calcd for $C_{11}H_{12}N_2S$: C, 64.7; H, 5.9; N, 13.7.

Found: C, 64.5; H, 6.0; 13.5%).

4d: Yield (65%); m.p. 258-260°C; IR (KBr) υ 3480, 3400 (NH), 2218 (CN); ^{1}H NMR (DMSO) δ 1.30 (m, 4H, $2CH_2$), 1.58 (s, 2H, CH_2), 2.39 (m, 2H, CH_2), 2.55 (s, 2H, CH_2), 2.80 (d, 2H, CH_2), 7.90 (s, 1H, pyridine H-4), 13.99 (s, br, 1H, NH); MS, m/e 218; (Calcd for $C_{12}H_{14}N_2S$: C, 66.1; H, 6.4; N, 12.8. Found: C, 66.0; H, 6.2; N, 12.5%).

4e: Yield (60%); m.p. 250°C; IR (KBr) υ 3420 (NH), 2220 (CN); ^{1}H NMR (DMSO) δ 1.22 (s, 4H, $2CH_2$), 1.38 (d, 6H, $3CH_2$), 1.66 (s, 2H, CH_2), 2.40 (d, 2H, CH_2), 2.70 (m, 2H, CH_2), 6.89 (s, 1H, pyridine H-4), 14.0 (s, br, 1H, NH); (Calcd for $C_{14}H_{18}N_2S$: C, 68.3; H, 7.3; H, 11.4. Found: C, 68.0; H, 7.1; N, 11.0%).

Cycloalkane ring-fused 3-cyano-2-(methylthio)pyridines 5a-e

A mixture of **4** (0.01 mol), NaOH (0.02 mol), and MeI (0.015 mol) in dry dichloromethane (50 ml) was stirred at room temperature for 24 h and then diluted with cold water (100 ml). The dichloromethane layer was washed several times with water, dried and then evaporated. The resulting solid product was collected by filtration and crystallized from the appropriate solvent.

5a: Yield (90%); m.p. 102-104°C (EtOH); IR (KBr) υ 2220 (CN); ^{1}H NMR (DMSO) δ 2.01 (t, 2H, CH_2), 2.40 (t, 2H, CH_2), 2.59 (s, 3H, SCH_3), 2.89 (t, 2H, CH_2), 7.92 (s, 1H, pyridine H-4); (Calcd for $C_{10}H_{10}N_2S$: C, 63.2; H, 5.3; N, 14.7. Found: C, 63.0; H, 5.0; N, 14.5%).

5b: Yield (88%), m.p. 91°C (EtOH); IR (KBr) υ 2222 (CN); ^{1}H NMR (DMSO) δ 1.65 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 2.53 (s, 3H, SCH_3), 2.67 (m, 2H, CH_2), 2.84 (m, 2H, CH_2), 7.85 (s, 1H, pyridine H-4); (Calcd for $C_{11}H_{12}N_2S$: C, 64.7; H, 5.9; N, 13.7. Found: C, 64.3; H, 6.0; N, 13.5%).

5c: Yield (76%); m.p. 83°C (MeOH); IR (KBr) υ 2218 (CN); ^{1}H NMR (DMSO) δ 1.45 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 1.77 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 2.58 (s, 3H, SCH_3), 2.89 (m, 2H, CH_2), 7.99 (s, 1H, pyridine H-4); M^+ m/e 218; (calcd for $C_{12}H_{14}N_2S$: C, 66.1; H, 6.4; N, 12.8. Found: C, 65.8; H, 6.5; N, 12.6%).

5d: Yield (50%), m.p. 89°C (MeOH), IR (KBr) υ 2223 (CN), ^{1}H NMR (DMSO) δ 1.33 (d, 4H, $2CH_2$), 1.55 (s, 2H, CH_2), 2.40 (d, 2H, CH_2), 2.51 (s, 2H, CH_2), 2.56 (s, 3H, SCH_3), 2.80 (d, 2H, CH_2), 7.96 (s, 1H, pyridine H-4); M^+ m/e 232; (Calcd for $C_{13}H_{16}N_2S$: C, 67.2; H, 6.9; N, 12.1. Found: C, 66.9; H, 6.7; N, 11.9%).

5e: Yield (55%), m.p. 113°C (EtOH); IR (KBr) υ 2220 (CN); ^{1}H NMR (DMSO) δ 1.24 (s, 4H, $2CH_2$), 1.42 (d, 6H, $3CH_2$), 1.73 (s, 2H, CH_2), 2.45 (m, 2H, CH_2), 2.58 (s, 3H, SCH_3), 2.93 (t, 2H, CH_2), 7.93 (s, 1H, pyridine H-4); M^+ m/e 260; (Calcd for $C_{15}H_{20}N_2S$: C, 69.2; H, 7.7; N, 10.8. Found: C, 68.9; H, 7.5; N, 10.5%).

Cycloalkane ring-fused 3-cyano-2-(methylsulfonyl)pyridines 6a-e

A mixture of **5** (0.01 mol) and m-chloroperbenzoic acid (0.03 mol) in ethanol (100 ml) was stirred for 5 h at room temperature and then concentrated in vacuo. The residue was dissolved in dichloromethane, and the solution was washed several times with 1% NaOH, dried and evaporated. The residue was crystallized from the appropriate solvent.

6a: Yield (50%), m.p. 76°C; IR (KBr) υ 2220 (CN); ^{1}H NMR ($CDCl_3$) δ 1.94 (m, 2H, CH_2), 2.64-2.99 (m, 4H, $2CH_2$), 3.35 (s, 3H, SO_2CH_3), 7.92 (s, 1H, pyridine H-4); (Calcd for $C_{10}H_{10}N_2SO_2$: C, 53.6, H, 4.5; N, 12.5. Found: C, 53.4; H, 4.2; N, 12.2%).

6b: Yield (40%), m.p. 66°C; IR (KBr) υ 2230 (CN); ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 2H, CH_2), 1.88 (m, 2H, CH_2), 2.76 (m, 2H, CH_2), 2.88 (m, 2H, CH_2), 3.33 (s, 3H, SO_2CH_3); 7.89 (s, 1H, pyridine H-4); (Calcd for $C_{11}H_{12}N_2SO_2$: C, 55.9; H, 5.1; N, 11.9. Found: C, 56.1; H, 4.9; N, 11.6%).

6c: Yield (40%); m.p. 72°C, IR (KBr) υ 2235 (CN); ^{1}H NMR ($CDCl_3$) δ 1.44-1.93 (m, 6H, $3CH_2$), 2.44-2.73 (m, 2H, CH_2), 2.88-3.05 (m, 2H, CH_2), 3.28 (s, 3H, SO_2CH_3), 7.97 (s, 1H, pyridine H-4); (Calcd for $C_{12}H_{14}N_2SO_2$: C, 57.6; H, 5.6; N, 11.2. Found: C, 57.5; H, 5.5; N, 10.9%).
6d: Yield (45%), m.p. 67°C; IR (KBr) υ 2210 (CN); ^{1}H NMR ($CDCl_3$) δ 1.38 (d, 4H, $2CH_2$), 1.69 (s, 2H, CH_2), 2.41 (d, 2H, CH_2), 2.53 (s, 2H, CH_2), 2.85 (d, 2H, CH_2), 3.30 (s, 3H, SO_2CH_3), 7.94 (s, 1H, pyridine H-4); (Calcd for $C_{13}H_{16}N_2SO_2$: C, 59.1; H, 6.1; N; 10.6. Found: C, 59.0; H, 5.8; N, 10.4.
6e: Yield (40%); m.p. 89°C; IR (KBr) υ 2215 (CN); ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 4H, $2CH_2$); 1.43 (d, 6H, $3CH_2$), 1.73 (s, 2H, CH_2), 2.58 (m, 2H, CH_2), 2.94 (t, 2H, CH_2), 3.31 (s, 3H, SO_2CH_3), 7.93 (s, 1H, pyridine H-4); (Calcd for $C_{15}H_{20}N_2SO_2$: C, 61.6; H, 6.8; N, 9.6. Found: C, 61.5; H, 6.5; N, 9.5%).

2,4-Diamino-5-deazapteridines 7a-e

A mixture of **6** (0.01 mol) and guanidine carbonate (0.01 mol) in diphenyl ether (50 ml) was heated at 170-175°C (bath temperature) for 3h. After cooling, the mixture was diluted with ether (50 ml). The precipitates were collected by filtration and crystallized from the appropriate solvent.
7a: Yield (50%); m.p. >300°C (DMF); IR (KBr) υ 3555, 3500, 3480 (NH_2); ^{1}H NMR (DMSO) δ 2.0 (t, 2H, CH_2), 2.41 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 6.11 (s, br, 2H, NH_2), 6.99 (s, br, 2H, NH_2), 7.97 (s, 1H, pyridine H-4); (Calcd for $C_{10}H_{11}N_5$: C, 59.7; H, 5.5; N, 34.8. Found: C, 59.4; H, 5.2; N, 34.5%).
7b: Yield (50%); m.p. >300°C (DMSO); IR (KBr) υ 3580, 3540, 3470, 3420 (NH_2); ^{1}HNMR (DMSO) δ 1.56 (t, 2H, CH_2), 1.60 (t, 2H, CH_2), 2.30 (t, 2H, CH_2), 2.74 (t, 2H, CH_2), 6.32 (s, br, 2H, NH_2), 7.16 (s, br, 2H, NH_2), 7.92 (s, 1H, pyridine H-4); (Calcd for $C_{11}H_{13}N_5$: C, 61.4, H, N, 32.6. Found: C, 61.1; H, 5.8; N, 32.3%).
7c: Yield (40%), m.p. >300°C (DMF); IR (KBr) υ 3520, 3460, 3430 (NH_2); ^{1}H NMR (DMSO) δ 1.38 (s, 2H, CH_2), 1.63 (s, 2H, CH_2), 1.70 (s, 2H, CH_2), 2.40 (d, 2H, CH_2), 2.90 (d, 2H, CH_2), 5.99 (s, br, 2H, NH_2), 6.98 (s, br, 2H, NH_2). 7.98 (s, 1H, pyridine H-4); (Calcd for $C_{12}H_{15}N_5$: C, 62.9; H, 6.6; N, 30.6. Found: C, 62.5; H, 6.2; N, 30.2%).
7d: Yield (55%); m.p. >300°C (dioxane); IR (KBr) υ 3480, 3400, 3370 (NH_2); ^{1}H NMR (DMSO) δ 1.38 (s, 6H, $3CH_2$), 1.73 (s, 2H, CH_2), 2.41 (d, 2H, CH_2), 2.80 (t, 2H, CH_2), 6.11 (s, br, 2H, NH_2), 7.03 (s, br, 2H, NH_2), 7.95 (s, 1H, pyridine H-4); (Calcd for $C_{13}H_{17}N_5$: C, 64.2; H, 6.7; N, 28.8. Found: C, 64.0; H, 6.5; N, 28.5%).
7e: Yield (50%); m.p. >300°C (dioxane); IR (KBr) υ 3560, 3470, 3420 (NH_2); ^{1}H NMR (DMSO) δ 1.22 (s, 4H, $2CH_2$), 1.40 (d, 6H, $3CH_2$), 1.68 (s, 2H, CH_2), 2.43 (d, 2H, CH_2), 2.75 (t, 2H, CH_2), 6.00 (s, br, 2H, NH_2), 7.10 (s, br, 2H, NH_2), 7.98 (s, 1H, pyridine H-4); (Calcd for $C_{15}H_{21}N_5$: C, 66.4; H, 7.8; N, 25.8. Found: C, 66.0; H, 7.5; N, 25.5%).

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