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Condensed heterocycles: Part I—Synthesis of pyrazolo, isoxazolo, pyrimido, pyranopyridinones and a novel bridgehead nitrogen heterocycle

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3-Cyano-5-formyl-6-hydroxy-1, 4-dimethyl-2(1*H*)-pyridinone **2** on reaction with hydrazine, phenyl hydrazine, hydroxylamine hydrochloride, urea and hippuric acid yields 1-substituted-5-cyano-4, 7-dimethyl-1*H*, 6*H*, 7*H*-pyrazolo[3, 4-*b*]pyridin-6-one **3a, 3b**, 5-cyano-4, 7-dimethyl-6*H*, 7*H*-isoxazolo[5, 4-*b*]pyridine-6-one **4**, 6-cyano-5, 8-dimethyl-1*H*, 2*H*, 7*H*, 8*H*-pyrido[2, 3-*d*]pyrimidine-2, 7-dione **6** and 3-benzoylamino-6-cyano-5, 8-dimethyl-2*H*, 7*H*, 8*H*-pyrano[2, 3-*b*]pyridin-2, 7-dione **7** respectively. 3-Cyano-6-hydroxy-1, 4-dimethyl-2(1*H*)-pyridinone **1** reacts with benzalacetophenone **8** to furnish 6-cyano-5, 8-dimethyl-2, 4-diphenyl-4*H*, 7*H*, 8*H*-pyran[2, 3-*b*]pyridin-7-one **9** in one step. 2-Carboxymethyl-4-ethoxymethylenyl-1, 2, 3, 4-tetrahydroisoquinolin-1, 3-dione **11** on reaction with hydrazine and phenyl hydrazine affords 3-substituted-4-carboxymethyl-4, 5-dihydropyrazolo[3, 4-*c*] isoquinolin-5-one **12a** and **12b**. **12a** on refluxing in acetic anhydride forms a new nitrogen bridged heterocycle, 4*H*, 5*H*, 7*H*-pyrazolo[4, 3; 3, 2: *l*, *m*]imidazo[3, 2-*b*] isoquinolin-4, 7-dione **13**. The structures have been elucidated on the basis of IR and ^{1}H-NMR spectral analysis.

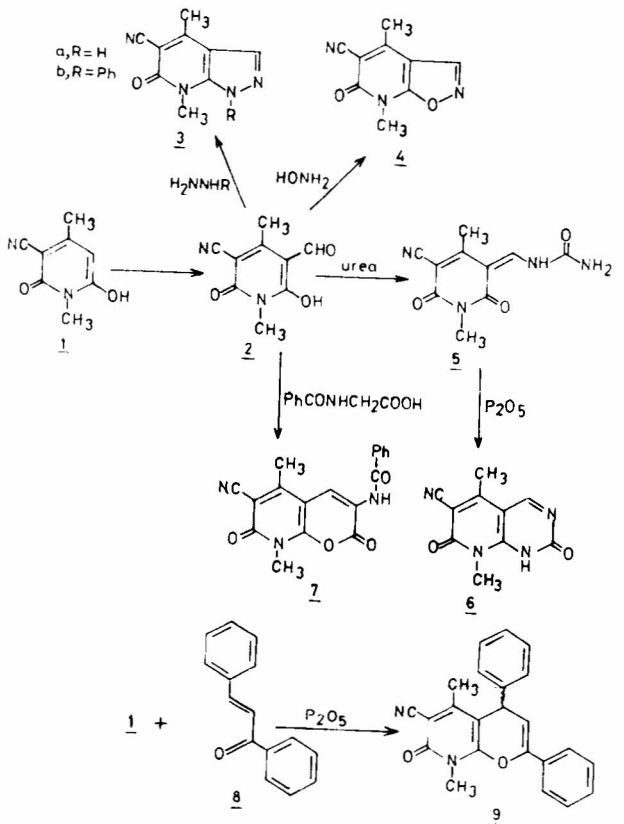
Substituted 2-pyridinones have gained unique importance due to their wide applicability in the field of dyestuff[1] and medicinal chemistry[2]. Pyrazoles, isoxazoles, pyrimidines and pyrans are also useful heterocyclic moieties as they possess a broad spectrum of biological activities such as antiviral[3], CNS depressant[4], bactericidal[5], ulcer inhibitor[6] etc. In view of this we report herein convenient syntheses of some new fused heteroycles incorporating the above moieties in 2-pyridinone ring system.

3-Cyano-6-hydroxy-1, 4-dimethyl-2(1H)-pyridinone **1**[7] on reaction with triethyl orthoformate underwent formylation to produce 3-cyano-5-formyl-6-hydroxy-1, 4-dimethyl-2(1*H*)-pyridinone **2** in good yield which when refluxed with hydrazine hydrate and phenyl hydrazine in a mixture of ethanol and acetic acid yielded 1-substituted 5-cyano-4, 7-dimethyl-1*H*, 6*H*, 7*H*-pyrazolo[3, 4-*b*]pyridin-6-one **3a, 3b**. Similarly the reaction of **2** with hydroxylamine hydrochloride, urea and hippuric acid gave 5-cyano-4, 7-dimethyl-6*H*, 7*H*-isoxozolo[5, 4-*b*]pyridin-6-one **4**, 3-cyano-1, 4-dimethyl-5-ureidomethylene-1*H*, 2*H*, 5*H*, 6*H*-pyridin-2, 6-dione **5** and 3-benzoylamino-6-cyano-5, 8-dimethyl-2*H*, 7*H*, 8*H*-pyrano[2, 3-*b*]pyridin-2, 7-dione **7**, respectively (Scheme I).

Compound **5** on heating with phosphorus pentoxide under anhyd. conditions underwent cyclisation to furnish a fused ring system; 6-cyano-5, 8-dimethyl-1*H*, 2*H*, 7*H*, 8*H*-pyrido[2, 3-*d*]pyrimidine-2, 7-dione **6**. Further, pyranopyridinone of the type 6-cyano-5, 8-dimethyl-2, 4-diphenyl-4*H*, 7*H*, 8*H*-pyrono[2, 3-*b*]pyridin-7-one **9** was also obtained in one pot synthesis from **1** by refluxing it with benzalacetophenone **8** in the presence of phosphorus pentoxide (Scheme I).

2-Carboxymethyl-1, 2, 3, 4-tetrahydroisoquinolin-1, 3-dione **10**[8] which contains an active methylene group at its 4-position was selected as another precurser to construct some more fused rings. **10** on refluxing with triethylorthoformate resulted in the formation of 2-carboxymethyl-4-ethoxymethylenyl-1, 2, 3, 4-tetrahydroisoquinolin-1, 3-dione **11** which on heating with hydrazine hydrate and phenyl hydrazine in a mixture of ethanol and acetic acid yielded 3-substituted-4-carboxymethyl-4, 5-dihydropyrazolo[3, 4-*c*]isoquinolin-5-one **12a** and **12b**. The reactive carboxymethyl grouping at the 4-position of **12a** was further exploited to obtain a new tetracyclic nitrogen bridged heterocycle, 4*H*, 5*H*, 7*H*-pyrazolo[4, 3; 3, 2:1, *m*]imidazo[3, 2-*b*]isoquinolin-4, 7-dione **13**. This was achieved by heating **12a** with acetic anhydride when intramolecular nucleophilic attack of $-NH-$ on $-COOH$ took place leading to cyclocondensation (Scheme II).

The spectral and elemental data of all the new



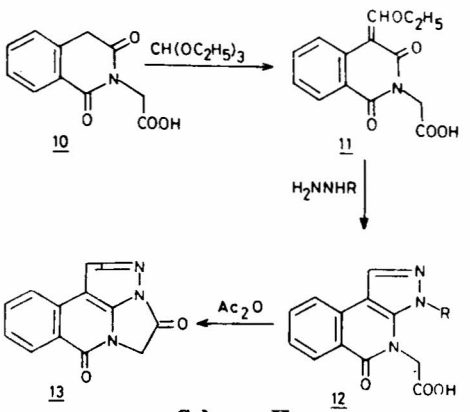
Scheme I

compounds are in conformity with the assigned structures and are given under the individual compounds in the Experimental Section.

Experimental Section

All the melting points are uncorrected and taken on Gallenkamp melting point apparatus. IR spectra were recorded on Jasco FTIR-5300 spectrometer and PMR spectra on VXR-300S Varian Supercon NMR spectrometer (300 MHz) using TMS as internal standard (chemical shift in δ, ppm).

3-Cyano-5-formyl-6-hydroxy-1, 4-dimethyl-2(1*H*)-pyridinone 2. A mixture of 3-cyano-6-hydroxy-1;4-dimethyl-2 (*1H*)-2-pyridinone **1** (1.64 g, 0.01 mole) and triethyl orthoformate (17 mL) was gently refluxed for 2 hr. On cooling the mixture the reddish pink product separated which was filtered, washed with hexane and crystallized from benzene-ethanol mixture, yield 85%, m.p. 153°C; IR(KBr): 3445 (OH), 2226 (−C≡N), 1684 (−CH=O), 1616 (>C=O, imidic); PMR ($CDCl_3$): δ 2.55 (s, 3H, C−CH_3), 3.38 (s, 3H, N−CH_3), 8.93 (s, 1H, −CHO), 15.12 (s, 1H, OH) (Found: C, 56.26; H, 4.15; N, 14.56. $C_9H_8N_2O_3$ requires C, 56.25; H, 4.16; N, 14.58%).



Scheme II

5-Cyano-4, 7-dimethyl-1-phenyl-1*H*, 6*H*, 7*H*-pyrazolo[3, 4-*b*]pyridin-6-one 3b. A mixture of **2** (0.96g, 0.005 mole) and phenyl hydrazine (0.75 ml, 0.0075 mole) was refluxed in ethanol-acetic acid mixture (15 mL) (2:1, v/v) for 1 hr. The bright yellow product separated was filtered, washed with hot ethanol and crystallized from acetic acid, yield 92%, m.p. 214-15°C; IR(KBr): 2218 (C≡N), 1628 (C=O); PMR (DMSO-d_6): δ 2.4 (s, 3H, C−CH_3), 3.2 (s, 3H, N−CH_3), 6.7-7.3 (m, 5H, Ar−H), 8.3 (s, 1H, C_3−H) (Found: C, 68.2; H, 4.53; N, 21.23. $C_{15}H_{12}N_4O$ requires C, 68.18; H, 4.54; N, 21.21%).

5-Cyano-4, 7-dimethyl-1*H*, 6*H*, 7*H*-pyrazolo[3, 4-*b*]pyridin-6-one 3a. It was prepared from **2** and hydrazine hydrate by using the above method, yield 88%, m.p. >300°C; IR (KBr): 3109 (−NH), 2228 (C≡N), 1616 (C=O) (Found: C, 57.43; H, 4.27; N, 29.76. $C_9H_8N_4O$ requires C, 57.44; H, 4.25; N, 29.78%).

5-Cyano-4,7-dimethyl-6*H*,7*H*-isoxazolo-3,4-*b*]pyridin-6-one 4. A mixture of **2** (0.96 g, 0.005 mole) and hydroxylamine hydrochloride (0.52 g, 0.0075 mole) was refluxed in ethanol-acetic acid mixture (15 mL) (2:1 v/v) for 1 hr. The product separated was filtered, washed with hot ethanol and crystallized from ethanol-dimethyl-formamide mixture, yield 92%, m.p. 213°C; IR(KBr): 2214 (C≡N), 1624 (C=O); PMR (DMSO-d_6): δ 2.2 (s, 3H, C–CH_3), 3.0 (s, 3H, N–CH_3), 8.15 (s, 1H, C_3–H) (Found: C, 57.12; H, 3.71; N, 22.21. $C_9H_7N_3O_2$ requires C, 57.14; H, 3.70; N, 22.22%).

3-Cyano-1, 4-dimethyl-5-ureidomethylene-1*H*, 5*H*-pyridin-2, 6-dione 5. A mixture of **2** (0.96, 0.005 mole) and urea (0.45 g, 0.0075 mole) was refluxed in ethanol-acetic acid mixture (15 mL) (2:1, v/v) for 1 hr. The silky off-white product separated was filtered, washed with hot ethanol and crystallized from acetonitrile, yield 90%, m.p.

290°C; IR(KBr): 3362, 3200 and 3038 ($-NH_2$ and $-NH$), 2226 ($C\equiv N$), 1767, 1670 and 1628 (three $C=O$); PMR (DMSO-d_6): δ 2.48 (s, 3H, $C-CH_3$), 3.18 (s, 3H, $N-CH_3$), 7.65 and 8.04 (2s, 2H, $-CO.NH_2$), 8.47 (d, 1H, $=CH-N$), 11.93 (d, 1H, NH) (Found: C, 51.27; H, 4.26; N, 23.95. $C_{10}H_{10}N_4O_3$ requires C, 51.28; H, 4.27; N, 23.93%).

6-Cyano-5, 8-dimethyl-1*H*, 2*H*, 7*H*, 8*H*-pyrido[2, 3-*d*]pyrimidine-2, 7-dione 6. A mixture of **5** (0.2 g) and phosphorus pentoxide (0.4 g) was fused in an oil-bath at 240°C for 1 hr. The fused mass was treated with water when the product separated. It was filtered, washed with water and crystallized from acetonitrile, yield 50%, m.p. 244-46°C; IR(KBr): 3428 (NH), 2226 ($C\equiv N$), 1640 and 1601 (two $C=O$); PMR (DMSO-d_6): δ 2.49 (s, 3H, $C-CH_3$), 3.18 (s, 3H, $N-CH_3$), 8.53 (s, 1H, $CH=N$), 9.85 (bs, 1H, NH) (Found: C, 55.52; H, 3.70; N, 25.93. $C_{10}H_8N_4O_2$ requires C, 55.55; H, 3.70; N, 25.92%).

3-Benzoylamino-6-cyano-5, 8-dimethyl-2*H*, 7*H*, 8*H*-pyrano[2,3-*b*]pyridin-2,7-dione 7. A mixture of **2** (0.96 g, 0.005 mole) and hippuric acid (1.34 g, 0.0075 mole) in ethanol-acetic acid mixture (15 mL) (2:1, v/v) was refluxed for 1 hr. The separated product was filtered, washed with hot ethanol and crystallized from ethanol-dimethyl formamide mixture, yield 80%, m.p. >300°C; IR(KBr): 3408.5 ($-NH$), 2224 ($C\equiv N$), 1726 (pyrano $C=O$), 1665 (pyridino $C=O$), 1628 (amido $C=O$); PMR (DMSO-d_6): δ2.59 (s, 3H, $C-CH_3$), 3.35 (s, 3H, $N-CH_3$), 7.54 and 7.96 (m, 5H, $Ar-H$), 8.43 (s, 1H, C_4-H), 10.0 (s, 1H, NH) (Found: C, 64.49; H, 3.85; N, 12.52. $C_{18}H_{13}N_3O_4$ requires C, 64.47; H, 3.88; N, 12.53%).

6-Cyano-5, 8-dimethyl-2, 4-diphenyl-4*H*, 7*H*, 8*H*-pyrano[2, 3-*b*]pyridin-7-one 9. A mixture of **1** (0.492 g, .003 mole), benzalacetophenone (0.624 g, .003 mole) and phosphorous pentoxide (1 g) in acetic acid (10 mL) was refluxed for 5 hr. The product separated out on cooling was filtered, washed with hot ethanol and crystallized from dimethyl formamide, yield 70%, m.p. 298°C; IR(KBr): 2218 ($C\equiv N$), 1655 ($C=O$); PMR (DMSO-d_6): δ 2.07 (s, 3H, $C-CH_3$), 3.65 (s, 3H, $N-CH_3$), 4.86 (d, 1H, C_3-H), 6.15 (d, 1H, C_4-H), 7.33-7.71 (m, 10H, $Ar-H$) (Found: C, 80.57; H, 4.46; N, 6.95. $C_{27}H_{18}O_2N_2$ requires C, 80.59; H, 4.47; N, 6.96%).

4-Ethoxymethylenyl-2-carboxymethyl-1, 2, 3, 4-tetrahydroisoquinolin-1, 3-dione 11. A mixture of 2-carboxymethyl-1, 2, 3, 4-tetrahydroisoquinolin-1, 3-dione **10** (2.19 g, 0.01 mole) and triethyl orthoformate (17 mL) was gently refluxed for 2 hr. Yellow solid separated on cooling the reaction mixture was filtered, washed with hexane and crystallized from benzene-ethanol mixture, yield 82%, m.p. 203°C; IR(KBr): 3134.6 (OH), 1746, 1694 and 1651 (three $C=O$); PMR (DMSO-d_6): δ1.43 (t, 3H, $-CH_3$), 4.55 (q, 2H, $-CH_2CH_3$), 4.60 (s, 2H, $-CH_2COOH$), 7.46 (dd, 1H, C_6H), 7.75(dd, 1H, $C-H$), 8.14 (d, 1H, C_5-H), 8.33 (d, 1H, C_8-H), 8.23 (s, 1H, $=CH-O-$), 12.94 (bs, 1H, OH) (Found: C, 61.10; H, 4.73; N, 5.11. $C_{14}H_{13}NO_5$ requires C, 61.09; H, 4.72; N, 5.09%).

4-Carboxymethyl-4, 5-dihydro-1*H*-pyrazolo[3, 4-*c*]isoquinolin-5-one 12a. A mixture of **11** (1.37 g, 0.005 mole) and hydrazine hydrate (0.5 mL, 0.0075 mole) in ethanol-acetic acid mixture (15 mL)(2:1 v/v) was refluxed for 1 hr. The bright orange coloured product separated was filtered, washed with hot ethanol and crystallized from benzene-dimethyl formamide mixture, yield 86%, m.p. >300°C; IR(KBr): 3443 (OH), 3088 (NH), 1734 (isoquinolinone $C=O$), 1663 (carboxy $C=O$); PMR (DMSO-d_6): δ 4.67 (s, 2H, $-CH_2-$), 7.27 (dd, 1H, C_3-H), 7.62 (dd, 1H, C_7-H), 7.98 (d, 1H, C_9-H), 8.07 (d, 1H, C_6-H), 8.81 (s, 1H, $-CH=N$) (Found: C, 59.29; H, 3.71; N, 17.27. $C_{12}H_9N_3O_3$ requires C, 59.25; H, 3.70; N, 17.28%).

4-Carboxymethyl-4, 5-dihydro-3-phenylpyrazolo[3,4-*c*]isoquinolin-5-one 12b was prepared from **11** and phenyl hydrazine using the same method as above, yield 80%, m.p. 218°C; IR(KBr): 3441 (OH), 1682 (isoquinolinone $C=O$), 1634 (carboxy $C=O$) (Found: C, 67.72; H, 4.08; N, 13.15. $C_{18}H_{13}N_3O_3$ requires C, 67.71; H, 4.07; N, 13.16%).

4*H*, 5*H*, 7*H*-pyrazolo[4, 3; 3, 2:1, *m*]imidazo[3, 2*b*]isoquinolin-4, 7-dione 13. A mixture of **12a** (1.12 g, 0.005 mole) and acetic anhydride (20 mL) was refluxed for 1 hr. The product separated was filtered, washed with ethanol and crystallized from benzene-dimethyl formamide mixture, yield 75%, m.p. >300°C; IR(KBr): 1842 and 1750 (two $C=O$) (Found: C, 64.1; H, 3.11; N, 18.65. $C_{12}H_7N_3O_2$ requires C, 64.0; H, 3.11; N, 18.66%).

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