# Derivatives of 2,3-Dihydrocyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10(1*H*)one

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The annulation of 2-amino-3-hydroxy-, 2-amino-3-carboxy-, and 2-amino-3-methylpyridine with ethyl cyclopentanone-2-carboxylate led to the 5-hydroxy-, **2**, 5-carboxy-, **3**, and 5-methyl-, **4**, derivatives of the 2,3-dihydrocyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10(1*H*)one heterocycle. Alkylation of **2** with α-bromotoluene gave the 5-benzyloxy derivative.

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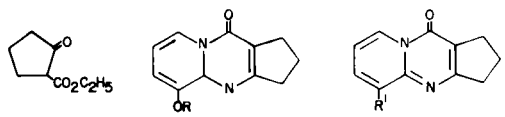
Over the past several years, we have reported on the annulation of variously substituted 2-aminopyridines with acetoacetic esters to give derivatives of the 4*H*-pyrido-[1,2-*a*]pyrimidin-4-one heterocycle (1a-e). The purpose of this article is to describe similar reactions involving the cyclic β-keto ester, ethyl cyclopentanone-2-carboxylate, **1**. With the appropriately substituted 2-aminopyridine, annulation was effected employing a large excess of **1** as solvent, or, employing two molar equivalents of **1** in solvents like diethylbenzene or ethyleneglycol monomethyl ether (1b, 2), and led to **2**, **3**, and **4** in good yield; alkylation of **2** with α-bromotoluene gave **5**.



**1** **2**, R = H; **5**, R = $CH_2C_6H_5$ **3**, $R^1$ = $CO_2H$; **4**, $R^1$ = $CH_3$

## EXPERIMENTAL

The microanalyses and spectra were obtained from the staff of the Analytical Department of This Institute employing instruments previously described (1a-e). The melting points were determined in capillary tubes in an electrically heated oil bath and are uncorrected.

2,3-Dihydro-5-hydroxycyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10-(1*H*) one (**2**).

A solution of 22.0 g. (0.2 mole) of 2-amino-3-pyridinol, 62.4 g. (0.4 mole) of **1**, and 200 ml. of diethylbenzene was stirred and heated by means of an oil bath maintained at *ca.* 150° for 1 hour and the oil bath temperature was gradually raised to 195° and maintained at that temperature for an additional 1 hour. The cooled diethylbenzene solution was decanted from a tar, and the solution concentrated, *in vacuo*, to give a residue of 29.8 g. This was recrystallized from 1400 ml. of Skellysolve E to give 22.4 g. (55% yield) of **2**, m.p. 153-155°; ir (deuteriochloroform): ν 3370(w), 1680(s), 1650(m), 1530(s), 1475(s), 1450(m), 1440(m), 1430(m) $cm^{-1}$; pmr (deuteriochloroform): δ 2.00-2.50 (m, 2H, $CH_2$ at position-2), 2.86-3.26 [t (J = 6 Hz), 4H, 2($CH_2$) at positions-1 and -3], 5.80 [s, 1H, *H*O (equilibrates with deuterium oxide)], 6.96-7.48 (m, 2H, 2*H* at positions-6 and -7), 8.64 [q (J = 3,9 Hz), 1H, *H* at position-8].

*Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.99; N, 13.85. Found: C, 65.20; H, 5.24; N, 13.77.

2,3-Dihydrocyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10(1*H*)one-5-carboxylic Acid (**3**).

A suspension of 5.0 g. (0.46 mole) of 2-aminonicotinic acid, 0.4 g. of *p*-toluenesulfonic acid, and 26 ml. of **1** was stirred by a magnetic bar and immersed in an oil bath preheated to 125°. The temperature of the oil bath was gradually raised and reached 178° in 1 hour when a clear solution formed. The temperature was maintained at 178-180° for 1 hour while 4 ml. of distillate was collected in a Dean-Stark trap attached to the reaction flask. The mixture was then cooled and the solid which crystallized was filtered and air-dried to give 6.2 g. of crude **3**, m.p. 187-192°. Recrystallization from 100 ml. of toluene gave 4.9 g. (46% yield) of product, m.p. 191-193°; ir (deuteriochloroform): ν 1700-2500 (broad s), 1720-1670 (broad s), 1575(s), 1530(s), 1500-1415 (broad s) $cm^{-1}$; pmr (deuteriochloroform): δ 2.10-2.60 (m, 2H, $CH_2$ at position-2), 2.85-3.85 (m, 4H, 2($CH_2$) at positions-1 and -3), 7.20-7.55 (m, 1H, 1*H* at position-7), 8.85, 9.75 [2q (J = 2,9 Hz), 2H, 2*H* at positions-6 and -8].

*Anal.* Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.99; H, 4.60; N, 12.09.

2,3-Dihydro-5-methylcyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10-(1*H*)one (**4**).

A solution of 10.8 g. (0.1 mole) of 2-amino-3-methylpyridine,

31.2 g. (0.2 mole) of **1**, and 250 ml. of ethyleneglycol monomethyl ether was heated under reflux for 40 hours, and then concentrated to dryness *in vacuo*. The crystalline residue, **14.2** g., was recrystallized from 425 ml. of cyclohexane to give 12.0 g. (60% yield) of **4**, m.p. 102-104°; ir (deuteriochloroform): $\nu$ 1690-1650 (broad s), 1625(s), 1570(s), 1525(s), 1480-1415 (broad s) $cm^{-1}$; pmr (deuteriochloroform): $\delta$ 2.00-2.50 (m, 2H, $CH_2$ at position-2), 2.62 (s, 3H, $CH_3$ at position-5), 2.90-3.30 (m, 4H, 2($CH_2$ at positions-1 and -3)), 6.85-7.70 (m, 2H, 2*H* at positions-7 and -8), 9.06 [q (J = 2,8 Hz), 1 H, *H* at position-6].

*Anal.* Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.81; H, 6.05; N, 13.81.

2,3-Dihydro-5-(benzyloxy)cyclopenta[*d*]pyrido[1,2-*a*]pyrimidin-10(1*H*)one (**5**).

A suspension of 6.1 g. (0.03 mole) of **2**, 9.9 g. of anhydrous potassium bicarbonate, 6.2 g. of α-bromotoluene, and 300 ml. of reagent grade 2-butanone was stirred and heated under reflux for 18 hours, cooled, and filtered with suction. The insoluble material was washed with 3-25 ml. portions of 2-butanone, the filtrate and washings were combined and concentrated *in vacuo* to give 10.0 g. of crude **5**. Recrystallization from 1 l. of cyclohexane gave 6.0 g. (68% yield) of pure **5**, m.p. 150-152°; ir (deuteriochloroform): $\nu$ 1690(s), 1625(m), 1615(w), 1575(w), 1530(m), 1501(w), 1470(s), 1450(m), 1425(m) $cm^{-1}$; pmr (deuteriochloroform): $\delta$ 2.00-2.50 (m, 2H, $CH_2$ at position-2), 2.86-3.44 [m, 4H, 2($CH_2$) at positions-1 and -3], 5.46 (s, 2H, $CH_2$Ph), 6.90-7.70, 8.60-8.85 (2 m, 8H, 5 Ar-*H* plus 3 Py-*H*).

*Anal.* Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.83; H, 5.52; N, 9.58. Found: C, 73.92; H, 5.80; N, 9.85.

## REFERENCES AND NOTES

(1a) H. L. Yale, B. Toeplitz, J. Z. Gougoutas, and M. Puar, *J. Heterocyclic Chem.*, **10**, 123 (1973); (b) H. L. Yale and J. T. Sheehan, *ibid.*, **10**, 143 (1973); (c) H. L. Yale, *ibid.*, **11**, 739 (1974); (d) H. L. Yale, *ibid.*, **12**, 427 (1975); (e) H. L. Yale and E. R. Sptizmiller, *ibid.*, **13**, 797 (1976).

(2) The single related synthesis to be found in the literature was that reported by K. Bowden and T. H. Brown, *J. Chem. Soc. (C)*, 2163 (1971), who reacted 2-aminopyridine with ethyl cyclohexanone-2-carboxylate in polyphosphoric acid ethyl ester and obtained the homologous 6,6,6-ring system derivative, **a**.