Saturated Heterocycles. Part 88.[1] Synthesis of a New Ring System: Dipyrido-[1,2-*a*:4,3-*d*]pyrimidin-11-one Derivatives

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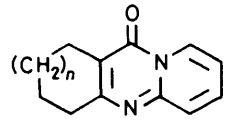
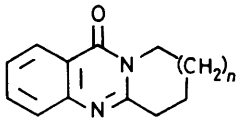
The synthesis of 1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one derivatives (**6a**—**s**), a new class of 'pyracridones', *i.e.* 2-azapyracridones, was performed by the condensation of 3-methoxycarbonyl-4-piperidones (**5**) and 2-aminopyridines in polyphosphoric acid. Catalytic reduction of compounds (**6**) or ring closure of (**5**) with 2-iminopiperidine was found to give the 1,2,3,4,6,7,8,9-octahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-ones (**7a**)—(**7c**). The seven-membered ring C homologue derivatives (**7d**), (**7e**) have also prepared by the latter method.

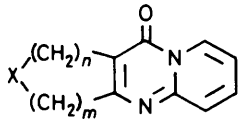
Pyracridones (11*H*-pyrido[2,1-*b*]quinazolin-11-ones), their ring A or ring C homologues (**1**) and (**2**), and their derivatives with different degrees of saturation are compounds of considerable chemical and pharmacological interest.[2–6] Pyracridone alkaloids,[7] frequently occur in Nature, and their homologues,[3] such as deoxyvasicinone and several analogous derivatives are being developed as drugs,[8] mainly as a result of their antiasthmatic and antiallergic activity.[8,9] The syntheses and biological actions[10,11] of the pyracridone analogues containing a hetero atom (O, NH, S) in ring A[10,12–16] (**3**) or ring C[11,17–21] (**4**) have been thoroughly studied. The synthesis of variously substituted pyracridones[22,23] (**1**), (**2**) and their partly or completely saturated derivatives[24,25] and stereochemical studies[26] on these compounds have also been published recently.



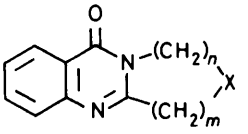
(**1**) *n* = 0,1,2



(**2**) *n* = 0, 1, 2, 3

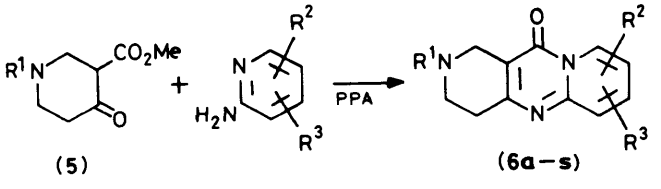


(**3**) X = NH, O, S



(**4**) X = NH, O, S

We now report the synthesis of a new family of the pyracridone group, *i.e.* 2-azapyracridones (**6**). The title compounds were synthesized from appropriately substituted 2-aminopyridines and 3-methoxycarbonyl-4-piperidone (**5**), or the *N*-benzyl and *N*-isopropyl derivative of the latter, by cyclization in polyphosphoric acid (PPA) (Scheme 1).

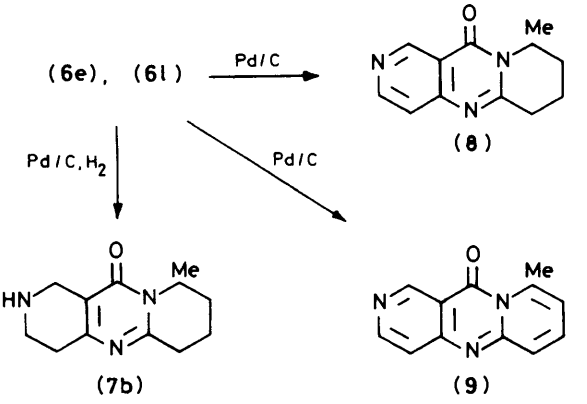


(**5**) (**6a**—**s**)

Scheme 1.

It is worth mentioning that cyclization by means of a mixture of phosphoryl chloride and PPA,[27] a method which can be used to much effect in the preparation of pyrido[2,1-*b*]quinazolin-11-ones[22] (**2**) and related pyrido[1,2-*a*]pyrimidin-4-ones, gives only very low yields (less than 10%) when applied to the synthesis of this ring system.

In a preliminary communication[28] we reported that 9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]-pyrimidin-11-one (**6e**) and the *N*-benzyl derivative (**6l**) undergo an intermolecular hydrogen-transfer reaction when heated in the presence of palladium-on-carbon catalyst, and two products, (**8**) and (**9**), are formed simultaneously (Scheme 2).



Scheme 2.

Through the use of a proton-donor or proton-acceptor solvent, the product ratio can be shifted in favour of (**8**) or of (**9**), respectively. In a proton-donor solvent (cyclohexene), the main product (**8**) is accompanied by the octahydro derivative (**7b**), which had also been prepared by the hydrogenation of (**6e**) in the presence of palladium-on-carbon catalyst.[28]

A further convenient synthetic route was developed for the preparation of compound (**7**) (Scheme 3). Reaction of 3-methoxycarbonyl-4-piperidones (**5**; R^1 = H, CH_2Ph) with cyclic amidines (**10**) in the presence of sodium ethoxide gave compounds (**7a**—**e**) in high yields. This method has the advantage over the reduction procedure that *N*-substituted derivatives can also readily be prepared by this means; further,

Table 1. U.v. and i.r. characteristics of representative dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-ones (**6**) and (**7**)

Compd.	$\lambda_{max.}$/nm (log ε)								$\nu_{max.}$/cm^{-1}
(**6a**)	334	(4.02)	249[a]	(3.98)	243	(4.04)	237[a]	(4.02)	3 400, 1 650, 1 460
(**6b**)	354	(4.02)	331[a]	(3.93)	255	(4.07)	249	(4.10)	3 450, 1 690, 1 500
(**6h**)	336	(4.10)	350[a]	(4.07)	243	(4.12)	238[a]	(4.10)	1 670, 1 630, 1 585
(**6i**)	354	(3.97)	325	(3.91)	254[a]	(4.00)	248	(4.02)	1 670, 1 480
	336	(4.12)	330[a]	(4.12)	250[a]	(4.07)	243	(4.14)	
(**6r**)	238[a]	(4.12)	214[a]	(4.30)					1 685, 1 485
(**6s**)	353	(4.09)	254[a]	(4.13)	249	(4.15)	218	(4.28)	1 690, 1 490
(**7a**)	273	(3.77)	231	(3.79)					3 400, 1 655, 1 535
(**7b**)	274	(3.78)	232	(3.81)					1 640, 1 515
(**7d**)	274	(4.07)	231	(4.08)					1 650, 1 540

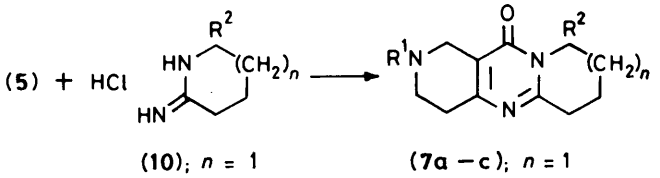
[a] Inflexion

Table 2. The ^{1}H n.m.r. characteristics of (**6**) and (**7**) representatives in $CDCl_3$

Compd.	Chemical shifts (p.p.m.) 1-H[a]	3-H[a]	4-H[a]	6-H[a]	7-H[a]	8-H[a]	9-H[a]	NR	Coupling constants (Hz)
(**6a**)	3.93s	3.16t	2.79t	7.47dd	7.61m	7.02dt	8.8dd	2.35s	$J_{8,9}$ = 6.61, $J_{7,9}$ = 0.60, $J_{6,7}$ = 9.07, $J_{6,8}$ = 0.92, $J_{7,8}$ = 6.58, $J_{3,4}$ = 5.41
(**6h**)	3.80s	2.96t	2.84t	7.51dd	7.60m	7.02dt	8.91dd	CH_2: 3.69s Ph: 7.3m	$J_{8,9}$ = 6.60, $J_{7,9}$ = 0.65, $J_{6,7}$ = 9.11, $J_{6,8}$ = 0.93, $J_{7,8}$ = 6.56, $J_{3,4}$ = 5.46
(**6r**)	3.74s	2.96t	2.88t	7.53dd	7.63m	7.06dt	8.97dd	Me: 1.19d CH: 2.99h	$J_{8,9}$ = 6.57, $J_{7,9}$ = 0.64, $J_{6,7}$ = 9.02, $J_{6,8}$ = 0.89, $J_{7,8}$ = 6.51, J_{34} = 5.37, $J_{Me,CH}$ = 6.56
(**6s**)	3.61s	2.83br s		7.27dd	7.33m	6.57dt	—	Me: 1.17d CH: 2.98h 9-Me: 3.04s	$J_{7,8}$ = 6.58, $J_{6,8}$ = 1.02, $J_{6,7}$ = 9.03, $J_{Me,CH}$ = 6.55
(**7a**)	3.81s	3.13t	2.63t	2.90t	1.95m		3.97t	2.88s	$J_{9,8}$ = 5.87, $J_{3,4}$ = 5.33, $J_{6,7}$ = 6.19
(**7c**)	3.73s	2.73br s		2.88t	1.9m		3.97t	CH_2: 3.50s Ph: 7.3m	$J_{9,8}$ = 5.93, $J_{6,7}$ = 6.14
(**7d**)[c]	3.93s	3.27t	2.77t	2.96t	1.87[b]m			3.54br s	$J_{10,9}$ = 5.9, $J_{3,4}$ = 5.41, $J_{6,7}$ = 6.00

[a] One or two hydrogens, respectively. [b] Three CH_2 protons with the same chemical shift. [c] 10-H_2 = 4.35t (p.p.m.).

by varying the ring size of the amidine (**10**), C-ring homologues too can be synthesized.



(**10**); *n* = 1 (**7a** – **c**); *n* = 1

(**11**); *n* = 2 (**7d** – **e**); *n* = 2

Scheme 3.

Spectroscopic Studies.—The i.r. and u.v. data on some characteristic representatives of the synthesized dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-ones (**6**) and (**7**) are listed in Table 1. Both the i.r. $\nu_{max.}$ and u.v. $\lambda_{max.}$ values are very close to those found for the analogous pyrido[2,1-*b*]quinazolin-11-one derivatives.[22] *N*-Substitution has no influence on $\lambda_{max.}$ but the presence of the 9-methyl group gives rise to a bathochromic shift of *ca.* 20 nm.

The 250 MHz ^{1}H n.m.r. data on some representatives of (**6**) and (**7**) are given in Table 2. It was found that in compounds (**6**) the aromatic part of the molecules can readily be identified *via* their spectra. In compounds (**6**) and (**7**), the saturated ring having a nitrogen in a bridgehead position and a bulky substituent at position-9 has a fixed conformation, while when there was no substituent we found (on the n.m.r. time scale) rapid conformational motion averaging the chemical shift difference between the *axial* and *equatorial* methylene protons. The A ring having a nitrogen atom is conformationally labile, even when attached to a bulky substituent.

Experimental

M.p.s were determined with a Boetius micro melting point apparatus and are uncorrected. The spectroscopic and analytical data on the compounds synthesized are given in Tables 1—4. The u.v. spectra were recorded in 95% ethanol ($c \sim 3 \times 10^{-5}$ g ml^{-1}) on a Unicam SP 800 spectrophotometer. The i.r. spectra were obtained in KBr pellets on a Unicam SP 200 instrument.

The 3-methoxycarbonyl-4-piperidones (**5**) were prepared as described by Morosawa.[29]

1,2,3,4-*Tetrahydro*-11H-*dipyrido*[1,2-a:4,3-d]*pyrimidin*-11-*one* (**6a**).—A mixture of 2-aminopyridine (0.9 g, 100 mmol), 3-methoxycarbonyl-4-piperidone hydrochloride (**5**; R^1 = H) (2 g, 10 mmol), and PPA (10 g) (Fluka) was stirred at 120 °C for 6 h. The reaction mixture was cooled to *ca.* 70 °C, water (10 ml) was added, and the mixture was neutralized with 10% aqueous sodium hydroxide during cooling in ice–water. The water-soluble products was extracted from the reaction mixture with chloroform (5 × 100 ml) and the combined extracts were dried (Na_2SO_4) and concentrated to give the required crystalline product (**6a**); *m/z* (%) 201 (*M*, 61), 200 (100), 172 (14), 144 (7), 131 (13), 78 (32), and 51 (8).

Compounds (**6b**—**g**) were prepared similarly. The *N*-benzyl derivatives (**6h**—**p**) which separated in the crystalline state on neutralization of the reaction mixture, were isolated by filtration. Compounds (**6r**) and (**6s**) appeared as oils after neutralization. Their extraction with chloroform was followed by purification of their dihydrochlorides, and liberation of the free bases.

Table 3. Physical and analytical data on 1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-ones (**6a—s**)

Compd.[a]	R^1	R^2	R^3	Yield (%)	M.p. (°C)	Formula (*M*)	Calcd./Found (%) C	H	N
(**6a**)	H	H	H	60	127—129[b]	$C_{11}H_{11}N_3O$ (201.22)	65.65 (65.95)	5.51 (5.5)	20.88 (20.3)
(**6b**)	H	6-Me	H	55	163—165[b]	$C_{12}H_{13}N_3O$ (215.24)	66.96 (66.75)	6.09 (6.35)	19.52 (19.25)
(**6c**)	H	7-Me	H	69	101—103[b]	$C_{12}H_{13}N_3O$ (215.24)	66.96 (66.8)	6.09 (6.1)	19.52 (19.3)
(**6d**)	H	8-Me	H	50	157—159[b]	$C_{12}H_{13}N_3O$ (215.24)	66.96 (66.6)	6.09 (6.5)	19.52 (19.95)
(**6f**)	H	7-Me	9-Me	50	174—176[b]	$C_{12}H_{15}N_3O$ (229.27)	68.10 (68.2)	6.59 (6.55)	18.33 (18.15)
(**6g**)	H	8-Cl	H	75	151—154[b]	$C_{10}H_{11}ClN_3O$ (235.67)	56.06 (56.75)	4.28 (4.45)	17.83 (18.1)
(**6h**)	$PhCH_2$	H	H	55	136—137[b]	$C_{18}H_{17}N_3O$ (291.36)	74.21 (74.5)	5.88 (5.75)	14.42 (14.35)
(**6i**)	$PhCH_2$	6-Me	H	55	145—147[b]	$C_{19}H_{19}N_3O$ (305.35)	74.73 (75.05)	6.27 (6.4)	1376 (13.6)
(**6j**)	$PhCH_2$	7-Me	H	59	78—81[b]	$C_{19}H_{19}N_3O$ (305.35)	74.73 (74.7)	6.27 (6.2)	13.76 (13.7)
(**6k**)	$PhCH_2$	8-Me	H	62	162—164[b]	$C_{19}H_{19}N_3O$ (305.35)	74.73 (74.45)	6.27 (7.25)	13.76 (14.0)
(**6m**)	$PhCH_2$	7-Me	9-Me	55	120—122[b]	$C_{20}H_{21}N_3O$ (319.39)	75.21 (75.0)	6.63 (6.9)	13.16 (13.3)
(**6n**)	$PhCH_2$	6-OH	H	60	170—171[b]	$C_{18}H_{17}N_3O_2$ (307.34)	70.34 (70.55)	5.58 (5.55)	13.67 (13.9)
(**6o**)	$PhCH_2$	8-Cl	H	62	176—177[b]	$C_{18}H_{16}ClN_3O$ (325.79)	66.36 (66.6)	4.95 (5.2)	12.90 (13.15)
(**6p**)	$PhCH_2$	8-Br	H	60	190—191[b]	$C_{18}H_{16}BrN_3O$ (370.25)	58.39 (58.25)	4.36 (4.75)	11.35 (11.0)
(**6r**)	Pr^i	H	H	57	70—71[c,d]	$C_{14}H_{17}N_3O$ (247.29)	69.11 (69.35)	7.04 (7.35)	17.27 (17.2)
(**6s**)	Pr^i	9-Me	H	64	80—81[c,e]	$C_{15}H_{19}N_3O$ (261.31)	70.01 (70.35)	7.44 (7.55)	16.33 (16.4)

[a] Compounds (**6e**; R^1 = H; R^2 = 9-Me) and (**6l**; R^1 = $PhCH_2$; R^2 = 9-Me) were described earlier.[28] [b] Recrystallized from ethyl acetate. [c] Recrystallized from hexane. [d] Dihydrochloride m.p. 264—267 °C. [e] Dihydrochloride m.p. 260—265 °C.

Table 4. Physical and analytical data on compounds (**7a—e**)

Compound	R^1	R^2	*n*	Yield (%) *a*	*b*	M.p. (°C) Solvent	Formula (*M*)	Calcd./Found (%) C	H	N
(**7a**)	H	H	1	50	92	111—113 ethyl acetate	$C_{11}H_{15}N_3O$ (205.25)	64.37 (64.7)	7.37 (7.6)	20.47 (20.65)
(**7b**)	H	Me	1	50	90[c]	105—108 di-isopropyl ether	$C_{12}H_{17}N_3O$ (219.28)	65.72 (65.4)	7.82 (8.1)	19.19 (19.35)
(**7c**)	$PhCH_2$	H	1	75		152—153 ethyl acetate	$C_{18}H_{21}N_3O$ (295.37)	73.19 (73.2)	7.17 (7.45)	14.23 (14.25)
(**7d**)	H	H	2	49		93—95 di-isopropyl ether	$C_{12}H_{17}N_3O$ (219.28)	65.72 (65.65)	7.82 (7.9)	19.16 (19.3)
(**7e**)	$PhCH_2$	H	2	60		120—122 acetone	$C_{19}H_{23}N_3O$ (309.39)	73.75 (74.1)	7.49 (8.0)	13.58 (13.1)

[a] By ring closure. [b] By reduction. [c] Described earlier.[28]

1,2,3,4,6,7,8,9-*Octahydro*-11H-*dipyrido*[1,2-a:4,3-d]*pyrimidin*-11-*one* (**7a**).—2-Benzyl-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**6l**) (0.5 g) was dissolved in methanol (50 ml) and reduced in hydrogen, at room temperature and atmospheric pressure, in the presence of 10% palladium-on-carbon catalyst. After the calculated vol. of hydrogen had been absorbed (3 h), the catalyst was filtered off. Concentration of the filtrate gave (**7a**) in crystalline form; *m/z* (%) 205 (*M*, 100), 204 (100), 177 (16), 176 (60), 82 (8.4), 80 (8.4), and 55 (9).

2-*Benzyl*-1,2,3,4,6,7,8,9-*octahydro*-11H-*dipyrido*[1,2-a:4,3-d]-*pyrimidin*-11-*one* (**7c**).—1-Benzyl-3-methoxycarbonyl-4-piperidone hydrochloride (**5**; R^1 = CH_2Ph) (2.8 g, 10 mmol) and 2-iminopiperidine hydrochloride (**10**; *n* = 1, R^2 = H) (1.35 g, 10 mmol) were dissolved in anhydrous ethanol (30 ml) and sodium (0.69 g, 30 mmol) was added to the solution. After 1 h the sodium chloride which separated was filtered off and the filtrate was refluxed for 7 h. After evaporation of the reaction mixture, the residue was suspended in water (30 ml) and the product was extracted with ether (4 × 30 ml). The combined

organic phases were dried (Na_2SO_4) and concentrated to give crystals of the octahydro compound (**7c**).

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