Saturated Heterocycles. 136 [1]. Synthesis of 2-Substituted 2-Azapyracridone Derivatives

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By means of substitution, addition and condensation on the secondary nitrogen of 9-methyl-1,2,3,4-tetrahydro-2-azapyracridone (**6**), twenty new azapyracridones were prepared.

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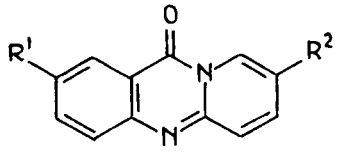
In a previous paper [2] we reported the synthesis of new dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (2-azapyracridone) derivatives. For several of these compounds a catalytic intermolecular hydrogen-transfer reaction was observed [3].

Many papers currently deal with the examination of pyrido[2,1-*b*]quinazolin-11-ones (pyracridones [4]), which have promising pharmacological properties (Figure 1). For instance, the 8-isopropylpyrido[2,1-*b*]quinazoline-2-carboxylic acid (**1**, R^1 = COOH and R^2 = isopropyl) exhibits a valuable anti-asthmatic effect [5a,b]. Some of the ring **C** homologues of pyracridone **2a** with favourable pharmacological effects have been isolated also from plants [6a-e]. The ring **A** homologues of pyracridones **2b** were recently synthesized [7a-d] for pharmacological [8a,b] and structural [9a,b] investigations.



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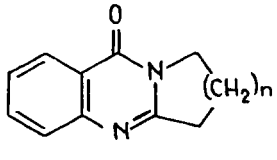
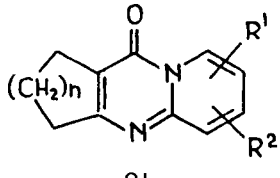


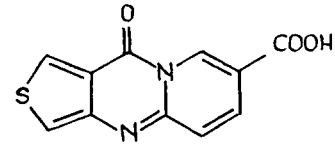
2a



2b

Figure 1

Compounds **3**, **4**, **5** and **6** with additional hetero atoms in ring **A** or **C** can be prepared analogously to the syntheses of **1** and **2**, but from heterocyclic starting materials (*e.g.* heterocyclic β-ketoesters, nicotinates, 2-aminopyridazines, etc.) (Figure 2). For the recently synthesized thieno[3,4-*d*]pyrido[1,2-*a*]pyrimidin-10-one-7-carboxylic acid (**3**), the starting material was a sulphur-containing β-ketoester [10]. Compound **3** and 11-oxopyridazino[3,2-*b*]-quinazoline-8-carboxylic acid (**5**) [11] have favourable anti-allergic and anti-asthmatic effects. Ring **C** homologues of compounds **4** have various pharmacological properties [12a-d].



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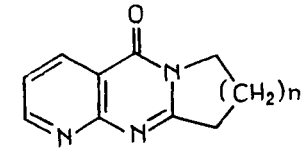

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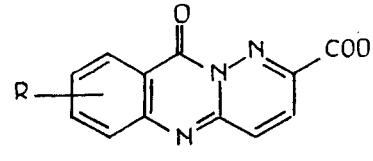

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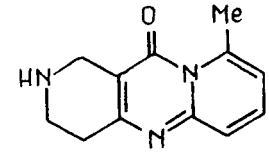
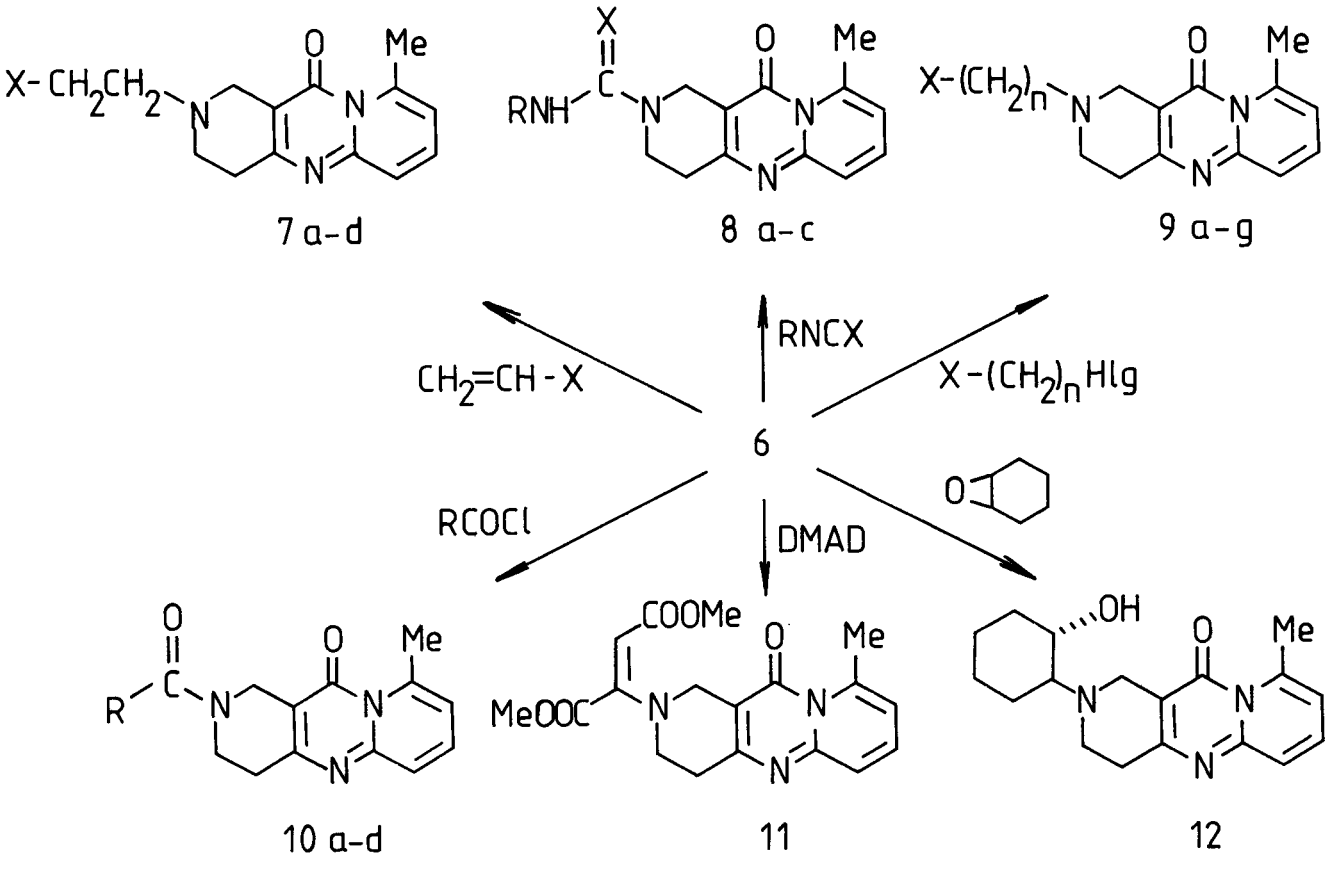


6

Figure 2

As a continuation of our synthetic work on bridgehead nitrogen-containing heterocycles [7a,9a,b], we now report some chemical transformation of 2-azapyracridones. 9-Methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**6**) was prepared in 95% yield by a modification of the earlier route [3]. The ring-closure reaction of 3-methoxycarbonyl-4-piperidone hydrochloride and 2-amino-6-methylpyridine was carried out in polyphosphoric acid. The reactivity of the secondary nitrogen in position 2 was examined in the reactions shown in the Scheme.

The methyl acrylate and acrylonitrile additions of **6** gave compounds **7a** and **7b**, according to anti-Markovnikov orientation (Table). Ester **7a** was reduced with lithium aluminum hydride to the 1,3-aminoalcohol **7c**; from **7a**



Scheme

with hydrazine hydrate, the hydrazide **7d** formed. Compound **6** could be transformed with isocyanates and isothiocyanates to derivatives of urea and thiourea **8a-c** even at room temperature. The secondary nitrogen reacted readily with alkyl halides in dry acetone in the presence of potassium carbonate, resulting in compounds **9a-g**. Compounds **10a-d** were formed by Schotten-Baumann acylation. Derivative **10e** was prepared from **10d** with *N*-methylpiperazine. A fast reaction was observed between **6** and dimethyl acetylenedicarboxylate (DMAD), while with cyclohexene oxide a slow addition took place to afford the *trans*-1,2-aminoalcohol **12**.

The 60 MHz ^{1}H nmr spectra corresponded to the structures given in the Scheme.

EXPERIMENTAL

Melting points were determined on a Boetius micro melting point apparatus and are uncorrected. The ir spectra were recorded in potassium bromide discs pills on a Unicam SP 200 spectrometer. Physical and analytical data on the compounds prepared are listed in the Table.

9-Methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**6**).

A mixture of 2-amino-6-methylpyridine (1.08 g, 10 mmoles) and 3-methoxycarbonyl-4-piperidone hydrochloride (1.94 g, 10 mmoles) was heated in polyphosphoric acid (10 g, FLUKA) for 6 hours, with stirring in an oil-bath at 120°. The mixture was then cooled to about 70° and water (10 ml) was added. After neutralization with 10% sodium hydroxide solution, the product was extracted with a mixture of chloroform-2-propanol 3:1 (3 x 100 ml). The combined extract was dried (sodium sulfate) and evaporated to afford 1.98 g (95%) of **6**, mp 135-136° (lit [2] yield 86%, mp 134-135°).

2-[(β-Methoxycarbonyl)-ethyl]-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**7a**).

A mixture of **6** (0.43 g, 2 mmoles) and methyl acrylate (0.17 g, 2 mmoles) in 20 ml of methanol was refluxed for 4 hours. After evaporation, the crude oily product **7a** was crystallized from di-isopropyl ether.

2(β-Cyanoethyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]-pyrimidin-11-one (**7b**).

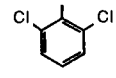
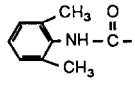
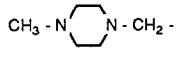
A mixture of **6** (0.43 g, 2 mmoles) and acrylonitrile (0.11 g, 2 mmoles) in 20 ml of methanol was refluxed for 3 hours. After removal of the solvent, the yellow crystalline residue **7b** was recrystallized from methanol.

2-(γ-Hydroxypropyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**7c**).

To a stirred suspension of lithium aluminum hydride (0.1 g) in 10 ml of dry THF, the ester **7a** (0.3 g, 1 mmole) was added under ice cooling. After 5 minutes, the mixture was worked up with the routine procedure. The crude oily product was crystallized from ethyl acetate.

2-(β-Hydrazidoethyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**7d**).

Table
Physical and Analytical Data of the 2-Aza-9-methyl-1,2,3,4-tetrahydropyracridones **7-12**

No.	X	n	R	Yield (%)	Mp (C°) solvent	Molecular formula	*Anal.* C(%)	(Calcd./Found) H(%)	N(%)	IR ν max (cm^{-1})
7a	CO_2CH_3	-	-	95	69 - 70 diisopropyl ether	$C_{16}H_{19}N_3O_3$	63.77 64.03	6.36 6.86	13.94 14.39	1470, 1650, 1720
7b	CN	-	-	90	164 - 166 methanol	$C_{15}H_{16}N_4O$	67.14 67.48	6.01 6.53	20.88 20.46	1490, 1680, 2300
7c [a]	CH_2OH	-	-	95	126 - 127 ethyl acetate	$C_{15}H_{19}N_5O_2$	65.91 66.20	7.01 7.27	15.37 15.59	1470, 1650, 3100
7d [b]	$CONHNH_2$	-	-	60	175 - 177 methanol	$C_{15}H_{19}N_5O_2$	59.79 60.00	6.35 6.92	23.24 23.50	1660, 3180, 3310
8a	O	-	Ph	95	204 - 205 benzene	$C_{19}H_{18}N_4O_2$	68.25 68.08	5.43 4.99	16.76 17.04	1480, 1660, 1620
8b	S	-	Ph	90	210 - 213 methanol	$C_{19}H_{18}N_4OS$	65.12 64.94	5.18 5.51	16.99 16.73	1480, 1660, 1520
8c	S	-		90	228 - 230 methanol	$C_{19}H_{16}Cl_2N_4OS$	54.42 54.34	3.85 4.20	13.36 12.95	780, 1480, 3220
9a	CO_2Et	1	-	80	74 - 75 diisopropyl ether	$C_{16}H_{19}N_3O_3$	63.77 63.50	6.36 6.64	13.36 13.60	1460, 1640, 1730
9b	CO_2Et	0	-	75	137 - 138 ethyl acetate	$C_{15}H_{17}N_3O_3$	62.70 62.98	5.97 6.25	14.63 14.94	1500, 1680, 1720
9c	CN	1	-	80	202 - 203 ethyl acetate	$C_{14}H_{14}N_4O$	66.12 66.59	5.55 5.54	22.03 21.86	1480, 1670, 2220
9d	$CH=CH_2$	1	-	80	97 - 96 diisopropyl ether	$C_{15}H_{17}N_3O$	70.56 70.38	6.71 7.04	16.46 16.53	1500, 1640, 1680
9e		1	-	75	185 - 186 ethanol	$C_{22}H_{24}N_4O_3$	70.19 70.32	6.43 6.20	14.88 14.95	1480, 1670, 3250
9f	Ph	1	-	85	146 - 147 [c] ethyl acetate	$C_{19}H_{19}N_3O$				1480, 1680, 2750
9g	*p*-BrPh	1	-	75	143 - 144 acetone	$C_{19}H_{18}BrN_3O$	59.38 59.37	4.72 5.06	10.94 10.85	800, 1490, 1670
10a	-	-	Ph	85	173 - 174 ethyl acetate	$C_{19}H_{17}N_3O_2$	71.45 72.06	5.27 5.82	13.16 13.37	1480, 1600, 1670
10b	-	-	*p*-BrPh	90	188 - 189 ethyl acetate	$C_{19}H_{16}BrN_3O_2$	57.30 57.54	4.05 4.35	10.55 10.80	1490, 1620, 1680
10c	-	-	*m*-ClPh	90	147 - 148 methanol	$C_{19}H_{16}ClN_3O_2$	64.50 64.10	4.56 4.50	11.80 11.57	1490, 1630, 1670
10d	-	-	CH_2Cl	85	161 - 162 ethyl acetate	$C_{14}H_{14}ClN_3O_2$	57.64 57.41	4.84 5.20	14.40 14.78	1490, 1620, 1660
10e [d]	-	-		65	177 - 180 diisopropyl ether	$C_{19}H_{25}N_5O_2$	64.20 64.53	7.09 7.50	19.71 19.88	1480, 1660, 2780
11	-	-	-	95	183 - 185 methanol	$C_{18}H_{19}N_3O_5$	60.50 60.00	5.36 5.53	11.76 12.05	1130, 1580, 1680
12	-	-	-	30	181 - 183 ethyl acetate	$C_{18}H_{23}N_3O_2$	68.98 68.89	7.40 7.31	13.41 12.94	1480, 1660, 3400

[a] Prepared from **7a** with lithium aluminum hydride. [b] Prepared from **7a** with hydrazine hydrate. [c] Lit [3] mp 146-147°.
[d] Prepared also from **10d** with *N*-methylpiperazine.

A mixture of **7a** (0.3 g, 1 mmole) and 5 ml of hydrazine hydrate (72%) was dissolved in 10 ml of methanol. After refluxing for 2 hours, the solvent was removed, the crude oily product was dissolved in 40 ml of chloroform, 40 ml of water was then added and the mixture was extracted with a further 2 x 40 ml of chloroform. The combined extract was dried (sodium sulfate) and evaporated to afford a yellow oil, which was crystallized from methanol.

2-Phenylcarbamoyl-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]-pyrimidin-11-one (**8a**).

A solution of **6** (0.43 g, 2 mmoles) and phenyl isocyanate (0.24 g, 2 mmoles) in 20 ml of benzene was allowed to stand overnight, and the solvent was then removed. The pale-yellow crystalline product **8a** was recrystallized from benzene.

2-Phenylthiocarbamoyl-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido-[1,2-*a*:4,3-*d*]pyrimidin-11-one (**8b**).

Compound **8b** was obtained as described for **8a**, starting from **6** (0.43 g, 2 mmoles) and phenyl isothiocyanate (0.27 g, 2 mmoles).

2-(*o*,*o'*-Dichlorophenylthiocarbamoyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**8c**).

This was prepared as described for **8a**, starting from **6** (0.43 g, 2 mmoles) and *o*,*o'*-dichlorophenyl isothiocyanate (0.41 g, 2 mmoles).

2-(Ethoxycarbonyl-methyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido-[1,2-*a*:4,3-*d*]pyrimidin-11-one (**9a**).

Anhydrous potassium carbonate (0.55 g, 4 mmoles) was suspended in a solution of **6** (0.43 g, 2 mmoles) and ethyl bromoacetate (0.33 g, 2 mmoles) in 50 ml of dry acetone. After stirring and refluxing for 5 hours, the suspension was cooled, and the inorganic salt was filtered off and washed with 3 x 5 ml of acetone. The solvent was removed, and the crude oily product **9a** was crystallized from di-isopropyl ether.

2-Ethoxycarbonyl-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]-pyrimidin-11-one (**9b**).

This obtained as described for **9a**, starting from **6** (0.43 g, 2 mmoles) and ethyl chloroformate (0.22 g, 2 mmoles).

2-Cyanomethyl-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]-pyrimidin-11-one (**9c**).

Compound **9c** was obtained as described for **9a**, starting from **6** (0.43 g, 2 mmoles) and chloracetonitrile (0.15 g, 2 mmoles).

2-Allyl-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**9d**).

This compound was obtained as described for **9a**, starting from **6** (0.43 g, 2 mmoles) and allyl bromide (0.24 g, 2 mmoles).

2-[(*o*,*o'*-Dimethyl)-2'-acetanilidyl]-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**9e**).

Compound **9e** was obtained as described for **9a**, starting from **6** (0.43 g, 2 mmoles) and α-bromo-(*o*,*o'*-dimethyl)-acetanilide (0.48 g, 2 mmoles).

2-Benzyl-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**9f**).

Compound **9f** was obtained as described for **9a**, starting from **6** (0.43 g, 2 mmoles) and benzyl bromide (0.34 g, 2 mmoles).

2-(*p*-Bromobenzyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]-pyrimidin-11-one (**9g**).

This was obtained as described for **9a**, starting from **6** (0.43 g, 2 mmoles) and *p*-bromobenzyl bromide (0.5 g, 2 g mmoles).

2-Benzoyl-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**10a**).

To a mixture of **6** (0.43 g, 2 mmoles), benzoyl chloride (0.28 g, 2.1 mmoles) and 2 *M* sodium hydroxide (2 ml, 4 mmoles), 50 ml of benzene was added. The mixture was stirred for 4 hours at ambient temperature. After this the organic layer was separated and dried (sodium sulfate), and the benzene was removed. The off-white crystalline product was recrystallized from ethyl acetate.

2-(*p*-Bromobenzoyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]-pyrimidin-11-one (**10b**).

This was obtained as described for **10a**, starting from **6** (0.43 g, 2 mmoles) and *p*-bromobenzoyl chloride (0.44 g, 2.1 mmoles).

2-(*m*-Chlorobenzoyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**10c**).

This was obtained as described for **10a**, starting from **6** (0.43 g, 2 mmoles), and *m*-chlorobenzoyl chloride (0.35 g, 2.1 mmoles).

2-Chloroacetyl-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]-pyrimidin-11-one (**10d**).

Compound **10d** was obtained as described for **10a**, starting from **6** (0.43 g, 2 mmoles) and chloroacetyl chloride (0.23 g, 2.1 mmoles).

2-[(1'-*N*-Methylpiperazyl)-acetyl]-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**10e**).

i) This compound was obtained as described for **10a**, starting from **6** (0.43 g, 2 mmoles) and (1-*N*-methylpiperazyl)acetyl chloride (0.35 g, 2.1 mmoles).

ii) A mixture of **10d** (0.58 g, 2 mmoles), *N*-methylpiperazine (0.2 g, 2 mmoles) and potassium carbonate (0.28 g, 4 mmoles) was suspended in 30 ml of toluene. After refluxing and stirring for 15 hours, the mixture was cooled. The inorganic salt was filtered off, and the product was crystallized from diisopropyl ether, yield, 75%, mp 178-180°.

2-(α,β-Dimethoxycarbonylvinyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**11**).

A solution of **6** (0.43 g, 2 mmoles) and dimethyl acetylenedicarboxylate (0.28 g, 2 mmoles) in 30 ml of methanol was allowed to stand at ambient temperature for 1 hour. After removal of the solvent, the crude yellow oily product was crystallized from methanol.

2-(*trans*-2'-Hydroxycyclohexyl)-9-methyl-1,2,3,4-tetrahydro-11*H*-dipyrido[1,2-*a*:4,3-*d*]pyrimidin-11-one (**12**).

A mixture of **6** (0.43 g, 2 mmoles) and cyclohexene oxide (0.39 g, 4 mmoles) was dissolved in 20 ml of methanol. After refluxing for 25 hours, the solvent was removed. To the crude oily residue, 30 ml of water was added. This was extracted with 3 x 50 ml of benzene. The combined extract was dried (sodium sulfate) and the benzene was removed. The crude yellow oily product was crystallized from ethyl acetate.

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