Nitrogen Bridgehead Compounds VIII (1,2). Ring Transformations IV (3). Synthesis and Reactions of 2,3-Cycloalkylene-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones

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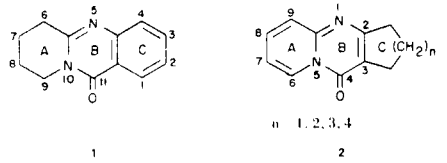
By condensing alicyclic β-ketocarboxylates with substituted 2-aminopyridines in polyphosphoric acid or phosphoryl chloride-polyphosphoric acid, numerous 2,3-tri-, tetra-, penta- and hexamethylene-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were synthesized for pharmacological purposes. The stability and several reactions of the title compounds were studied. The 6-substituted-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones were transformed into 1,8-naphthyridines in good yields independent of the ring size of ring **C**. The characteristic differences in the ir and uv spectra of the pyrido-pyrimidines and the corresponding naphthyridines are discussed. Catalytic hydrogenation of the pyrido[1,2-*a*]pyrimidin-4-ones furnished the corresponding 6,7,8,9-tetrahydropyrido-[1,2-*a*]pyrimidin-4-one derivatives. It was found that the **A** and **C** rings attached to the pyrimidinone ring in solutions of unsubstituted tetrahydropyrido[1,2-*a*]pyrimidin-4-ones are flexible, whereas in the 6-methyl derivatives the conformer containing the 6-methyl group in *axial* position predominates.

J. Heterocyclic Chem., 16, 137 (1979).

Earlier we have reported on the synthesis and reactions (4,5), rearrangement (6,7) and pharmacological investigations (8) of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives possessing valuable pharmacological properties. The derivatives of 6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylic acids appeared to be advantageous analgesic agents, but facile ring opening of these compounds (4) hindered their therapeutical use. On the basis of our earlier investigations it was expected that 2,3-cycloalkylene-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**2**) would be considerably more stable in aqueous solutions than the formerly prepared derivatives, while maintaining the analgesic activity.

The present work deals with the applicability of the methods used in the synthesis of pyrido[1,2-*a*]pyrimidines for synthesizing compounds of types **2**; also, some reactions of the new compounds have been compared with those of other pyrido[1,2-*a*]pyrimidin-4-ones.

Although the pyrido[2,1-*b*]quinazoline moiety (**1**) is present in various alkaloids isolated from a number of plants (*Mackinlaya subulate, Mackinlaya macrosciadia, Peganum harmala, Adhatoda vasica and Evodia rutascarpa*) (9), hardly any attention has been paid to the related 2,3-polymethylene-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**2**) (10) (Figure 1).



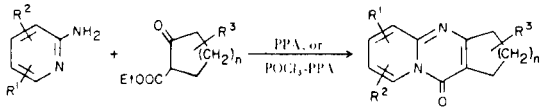
n = 1, 2, 3, 4

1 2

Figure 1

Synthesis.

The thermal ring closure reaction of β-ketocarbocylic esters with 2-aminopyridines leading to pyrido[1,2-*a*]-pyrimidin-4-ones has been known for a long time (11). In contrast with the 30-50% yields of the earlier thermal cyclization, condensations with the aid of polyphosphoric acid (PPA) as described by Shur and Israelstam (12), or by our method, *i.e.*, by using phosphoryl chloride and polyphosphoric acid (4) afford the desired products in yields which are higher by a factor of 30-40% (Figure 2).



3a-v

R^1 = H, CH_3, OH, Cl, NO_2; R^2 = H, CH_3; R^3 = H, CH_3, $C(CH_3)_3$; n = 1, 2, 3, 4

Figure 2

0022-152X/79/010137-08$02.25

The condensation of the substituted 2-aminopyridines and the 5-8 membered cyclic β-ketoesters in PPA or phosphoryl chloride-PPA was carried out at 100-120°, with reaction periods of 1-3 hours, the yields being 60-90%. Starting with ethyl 2-oxo-5-methylcyclopentane-1-carboxylate (13) or with the 2-oxo-4-*t*-butyl analogue (14), the derivatives substituted in ring **C** were similarly obtained in good yields. When using 6-substituted 2-aminopyridines, ring closure could only be effected with the 6-methyl derivative. The attempted reaction of 6-acetamino- and 6-hydroxy-2-aminopyridine with ethyl 2-oxocyclopentane-1-carboxylate led in both cases (PPA and phosphoryl chloride-PPA) only to decomposition products.

Although the synthesis of 2,3-tetramethylene-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**3b**, n = 2, $R^1 = R^2 = R^3 = H$) by the reaction of methyl 2-pyrrolidinocyclohexene-1-carboxylate with 2-aminopyridine had been described in 1970 by Halleux and Viehe (15), one year later Bowden and Brown (16) reported compound **3b**, obtained by the condensation of ethyl 2-oxocyclohexane-1-carboxylate and 2-aminopyridine in ethyl polyphosphate (PPEt), as a new compound, and the chemical shift value given by the latter authors for the 6-CH proton is incorrect.

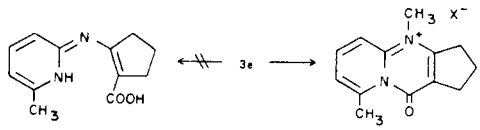
The report of Yale (17,18) reached us after we also had prepared the 2,3-trimethylene-9-methyl-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (**3n**) and its 2,3-trimethylene-9-hydroxy analogue (**3p**) described by Yale. By our procedure these compounds could be synthesized in 10-15% higher yields.

Cyclohexanone-2-carboxamide, readily prepared from cyclohexanone (19), gave, with 2-aminopyridine in PPA, compound **3b** (n = 2, $R^1 = R^2 = R^3 = H$) in a yield of 46%. When using phosphoryl chloride-PPA, however, **3b** was formed only in traces. To our knowledge, this procedure has not been applied thus far for the synthesis of pyrido[1,2-*a*]pyrimidin-4-ones.

Potts and co-workers (20) effected a ring closure reaction of 2-aminopyridine hydroiodide with ethyl acetoacetate in pyridine. This method was also successfully applied by us for cyclic ketoesters. When using other hydrogen halides (hydrogen chloride, hydrogen bromide) the ring closure reaction proceeded, but the yields were lower and the products less pure.

Characterization and Reactions of the Compounds.

The prepared pyrido[1,2-*a*]pyrimidin-4-ones (**3**) are readily crystallizing, light beige coloured or colourless crystalline substances, insoluble in water and usually readily soluble in organic solvents. In accordance with our expectations, their stability considerably surpasses that of the pyrido[1,2-*a*]pyrimidin-4-one-3-carboxylic acid derivatives. No ring opening was observed even upon heating the compounds under reflux for several days in water or in 5% hydrochloric acid (Figure 3).

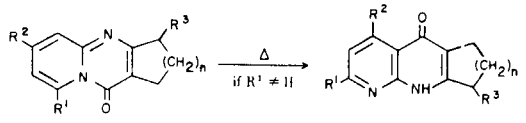


4a, X = I
4b, X = CH_3SO_4

Figure 3

The compounds have low basicity, and although their hydrochlorides can be precipitated, the base is liberated upon heating at temperature around their melting points, or in some cases even in aqueous solution. For example, when the recrystallization of the hydrochloride of the 7-nitro derivative **3u** (n = 1) is attempted from ethanol, the base crystallizes from the solution. The quaternary salts of **3e** (n = 1, R^1 = 6-Me, $R^2 = R^3 = H$) can be prepared in good yields by refluxing the compound with dimethyl sulfate in acetone, or by heating with methyl iodide at 100° in a sealed tube.

The thermal isomerization of some 6-substituted-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones yielding 1,8-naphthyridines has been reported earlier by us (6,7). The same reaction can also be achieved starting with the related tricyclic derivatives. The 6-methyl derivatives (**3**, n = 1, 2, 3, 4), could be isomerized at 300° in paraffin oil in nearly 100% yields. Under preparative conditions, the rate of the isomerization was found to be independent of the ring size of ring **C**. In spite of the high temperature, the naphthyridines (**5a-f**) were obtained in high purity (Figure 4).



3e-j 5a-f

$R^1 = CH_3$; $R^2 = H, CH_3$; $R^3 = H, CH_3$; n = 1, 2, 3, 4

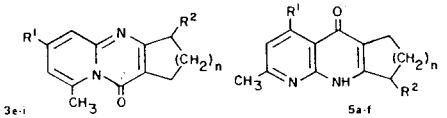
Figure 4

The solubility, melting points, ir and uv spectra of the 1,8-naphthyridines differ characteristically from those of the corresponding pyrido[1,2-*a*]pyrimidin-4-ones (7). The naphthyridines **5a-f** are very sparingly soluble in organic solvents, and they usually melt above 300°. The highest wavelength maximum in the uv spectra of the pyrido[1,2-*a*]pyrimidines appears above 350 nm, while that of the naphthyridines below 340 nm. The characteristic bands in the ir spectra of the pyrido[1,2-*a*]pyrimidin-4-ones can be identified at wavenumbers higher by 30-40 cm^{-1} (Table I).

It has been reported that in the presence of palladium on charcoal catalyst the derivatives containing no carboxyl function in position 3, and the 6-substituted pyrido[1,2-*a*]pyrimidine-3-carboxylic acid derivatives, can be satu-

Table I

Uv and Ir Spectra of Compounds **3e-j** and **5a-f**

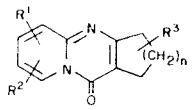


Compound No.	n	R^1	R^2	Absorption Maxima (nm) (log ε)				ν CH_2	ν C=O	Skeletal Vibrations (cm^{-1}) (a)		
3e	1	H	H	357 (3.95)	326.5 (3.81)	260 (4.07)	253 (4.12)	2940 (m)	1685 (vs)	1635 (m)	1590 (m)	1495 (vs)
3f	2	H	H	355 (3.92)	258.5 (4.07)	251 (4.12)		2950 (m)	1670 (vs)	1635 (m)	1585 (m)	1490 (vs)
3g	3	H	H	362 (3.97)	263 (4.06)	254 (4.10)	245 (4.05)	2940 (m)	1675 (vs)	1635 (m)	1585 (m)	1490 (vs)
3h	4	H	H	360 (3.98)	260.5 (4.05)	252.5 (4.10)		2935 (s)	1665 (vs)	1635 (m)	1585 (m)	1490 (vs)
3i	1	CH_3	H	350 (4.13)	248.5 (4.14)			2950 (m)	1685 (vs)	1645 (m)	1585 (w)	1485 (s)
3j	1	H	CH_3	357 (3.93)	252 (4.06)			2930 (m)	1680 (vs)	1630 (m)	1585 (m)	1480 (vs)
5a	1	H	H	328 (4.01)	289.5 (3.71)	278 (3.65)	248 (4.40)	2910 (s)	1605 (vs)	1580 (vs)	1520 (s)	1455 (m)
5b	2	H	H	343 (3.99)	288.5 (3.64)	279 (3.66)	249 (4.48)	2915 (s)	1610 (vs)	1575 (vs)	1525 (vs)	1455 (m)
5c	3	H	H	334.5 (4.01)	292.5 (3.59)	281.5 (3.61)	254 (4.49)	2905 (s)	1610 (vs)	1565 (s)	1520 (vs)	1460 (s)
5d	4	H	H	335.5 (3.94)	291 (3.52)	280 (3.54)	253 (4.43)	2905 (s)	1610 (vs)	1565 (s)	1525 (s)	1455 (s)
5e	1	CH_3	H	324 (3.88)	276 (3.20)	250 (4.18)		2920 (s)	1605 (vs)	1575 (vs)	1525 (s)	1455 (w)
5f	1	H	CH_3	328 (3.98)	289 (3.68)	247 (4.38)		2920 (s)	1605 (vs)	1575 (vs)	1520 (s)	1455 (m)

(a) Abbreviations: vs = very strong; s = strong; m = medium; w = weak.

Table II

Melting Points and Analytical Data for Compounds **3a-v**



Compound No.	n	Substituent	M.p., °C	Recrystallization Solvent (a)	Yield, % (b)	Molecular Formula	Analyses Calcd. C	H	N	Cl	Found C	H	N	Cl
3a	1	--	152-153	Isopropyl Ether	66	$C_{11}H_{10}N_2O$	70.95	5.41	15.05	--	70.78	5.67	15.26	--
			165-167		64	$C_{11}H_{11}ClN_2O$	59.33	4.98		15.92	59.00	5.15		16.01
3b	2	--	103-104 (c)	Isopropyl Ether	86 (c)	$C_{12}H_{12}N_2O$	71.98	6.04	13.99	--	71.87	6.09	14.02	--
			178-183		77	$C_{12}H_{13}ClN_2O$	60.89	5.54		14.98	60.56	5.56		14.91
3c	3	--	136	Ethyl Acetate	84	$C_{13}H_{14}N_2O$	72.86	6.59	13.08	--	72.63	6.98	12.95	--
			175-161		81	$C_{13}H_{14}N_2O$	62.27	6.03		14.14	62.20	5.77		14.08

Table II (continued)

Compound No.	n	Substituent	M.p., °C	Recrystallization Solvent (a)	Yield % (b)	Molecular Formula	Analyses Calcd. C	H	N	Cl	Found C	H	N	Cl
3d	4	--	114-115	Isopropyl Ether	66	$C_{14}H_{16}N_2O$	73.65	7.06	12.27	--	73.65	6.94	12.44	
			193-203		62	$C_{14}H_{17}ClN_2O$	63.51	6.47		13.39	63.20	6.03		13.18
3e	1	6-CH_3	160.5	Ethanol	84	$C_{12}H_{12}N_2O$	71.98	6.04	13.99	--	71.75	6.27	14.37	--
			221-224		67	$C_{12}H_{13}ClN_2O$	60.89	5.54		14.98	60.45	5.00		14.51
3f	2	6-CH_3	122-123	Ethanol	67	$C_{13}H_{14}N_2O$	72.86	6.59	13.08	--	72.60	6.87	13.16	--
			211-218		62	$C_{13}H_{15}ClN_2O$	62.27	6.03		14.14	61.82	6.05		14.09
3g	3	6-CH_3	97-98	Isopropyl Ether	61	$C_{14}H_{16}N_2O$	73.65	7.06	12.27	--	73.50	7.20	12.66	--
			222-227		58	$C_{14}H_{17}ClN_2O$	63.51	6.47		13.39	63.85	6.52		13.45
3h	4	6-CH_3	102	Ethanol-Water	75	$C_{15}H_{18}N_2O$	74.35	7.49	11.56	--	74.20	7.32	11.39	--
			200-206		68	$C_{15}H_{19}ClN_2O$	64.62	6.87		12.72	64.95	6.99		12.64
3i	1	6-CH_3	163-164	Ethanol	81	$C_{13}H_{14}N_2O$	72.86	6.59	13.08	--	72.90	6.59	12.76	--
		8-CH_3	190-203		72	$C_{13}H_{15}ClN_2O$	62.27	6.03		14.14	62.42	6.14		13.92
3j	1	1'-CH_3	86-87	Ethyl Ether	76	$C_{13}H_{14}N_2O$	72.86	6.59	13.08	--	72.74	6.71	13.12	--
		6-CH_3	178-188		68	$C_{13}H_{15}ClN_2O$	62.27	6.03		14.14	61.90	6.10		13.95
3k	1	2'-*t*-Bu	147	Ethyl Ether	57	$C_{16}H_{20}N_2O$	74.96	7.86	10.93	--	74.87	7.92	11.12	--
			195-200		45	$C_{16}H_{21}ClN_2O$	65.63	7.23		12.11	65.38	7.09		12.25
3l	1	7-CH_3	145-146	Ethanol	72 (d)	$C_{12}H_{12}N_2O$	71.98	6.04	13.99	--	71.70	6.25	13.72	--
			206-215		86	$C_{12}H_{13}ClN_2O$	60.89	5.54		14.98	60174	5.25		14.64
3m	1	8-CH_3	168-169	Ethanol	84	$C_{12}H_{12}N_2O$	71.98	6.04	13.99	--	72.04	6.02	13.76	--
			202-210		80	$C_{12}H_{13}ClN_2O$	60.89	5.54		14.98	60.71	5.55		14.99
3n	1	9-CH_3	109 (c)	Ethanol	81 (e)	$C_{12}H_{12}N_2O$	71.98	6.04	13.99	--	71.79	6.12	13.78	--
			170-180		77	$C_{12}H_{13}ClN_2O$	60.89	5.54		14.98	60.75	5.47		14.61
3o	1	7-Cl	151-152	Ethanol	82	$C_{11}H_9ClN_2O$	59.88	4.11	12.69	--	59.68	3.98	13.18	--
			203-206		76	$C_{11}H_{10}Cl_2N_2O$	51.39	3.92		13.79	51.39	4.00		13.51
3p	1	9-OH	159 (f)	Ethanol (70%)	69 (f)	$C_{11}H_{10}N_2O_2$	65.33	4.98	13.86	--	65.22	5.12	13.74	--
3r	2	9-OH	129	Ethanol (70%)	71	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.96	--	66.72	5.64	13.00	--
3s	3	9-OH	137-138	Ethanol (70%)	64	$C_{13}H_{14}N_2O_2$	68.00	5.84	11.70	--	68.07	5.92	11.94	--
3t	4	9-OH	156-157	Ethanol (70%)	62	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	--	69.42	6.54	11.23	--
3u	1	1-NO_2	168-169	Ethanol	45	$C_{11}H_9N_3O_3$	57.14	3.92	18.18	--	56.84	4.13	17.70	--
3v (g)	1	7-NH_2	260-264	Ethanol	35	$C_{11}H_{11}N_3O$	65.67	5.51	20.88	--	65.70	5.52	20.90	--

(a) The hydrochlorides were recrystallized from ethanol-ether. (b) In the case of the free bases yields refer to reactions in PPA, while in that of the hydrochlorides to phosphoryl chloride-PPA followed by decomposition by ethanol. (c) Lit. (15) m.p. 99-102°, yield 60%; lit. (16) m.p. 101.5-103°, yield 50%. (d) The product was isolated by extraction of the reaction mixture with chloroform. (e) Lit. (18) m.p. 102-104°, yield 60%. (f) Lit. (18) m.p. 153-155°, yield 55%. (g) Compound **3v** was prepared by the Béchamps reduction of **3u**.

rated to yield 6,7,8,9-tetrahydro analogues, whereas 6-unsubstituted pyrido[1,2-*a*]pyrimidine-3-carboxylic acid derivatives lead to the 1,6,7,8,9,9a-hexahydro analogues (4,5). Similarly, the tricyclic pyrido[1,2-*a*]pyrimidin-4-ones **3** can easily be saturated catalytically. Hydrogenation of the 6-substituted as well as of the 6-unsubstituted derivatives is completed in the presence of palladium on charcoal or Raney-nickel catalyst at room temperature and atmospheric pressure within 4-6 hours, and at higher temperature and under higher pressure within a few minutes by taking up two moles of hydrogen; in each case the 6,7,8,9-tetrahydro derivative (**6a-j**) is obtained in 100% yield (Figure 5).

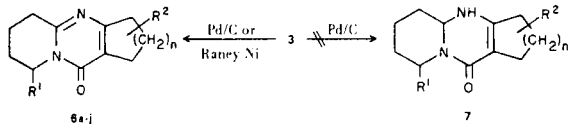


Figure 5

Similar to the pyrido[1,2-*a*]pyrimidines containing no carboxyl function in position 3 (5), the C=N double bond of the obtained tetrahydro derivatives **6** is not activated, and cannot be saturated under the conditions of the above catalytic hydrogenation or with sodium borohydride.

Ning and co-workers (21) prepared **6b** (n = 2, R^1 = R^2 = H) from **8** in a photochemical reaction, and synthesized it in an unambiguous route, by the reaction of 2-iminopiperidine hydrochloride with ethyl 2-cyclohexanon-1-carboxylate in 14% yield. We found that the reaction of the iminopiperidine base, liberated with sodium ethoxide *in situ*, with the corresponding ketoester in ethanol under reflux gave **6b** in a yield higher than 70% (Figure 6).

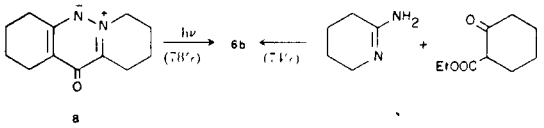


Figure 6

Conformational Studies.

According to X-ray diffraction studies of Ning and co-workers, ring B in the hydrobromide of **6b** is quasi-planar, while rings **A** and **C** are in the twisted boat conformation.

We have found that the chemical shifts of the *axial* and *equatorial* protons of the four methylene groups attached to the pyrimidinone ring ($N\text{-}CH_2\text{=}C\text{-}CH_2$, $CH_2\text{-}C\text{=}C\text{-}CH_2$) are nearly the same in the pmr spectrum of **6b** recorded in deuteriochloroform. This suggests that in solution rings **A** and **C** are flexible, and the observed averaging is due to the rapid conformational movement. The pmr spectra of the trimethylene, pentamethylene and hexamethylene derivatives (**6**, n = 1, 3, 4) can be interpreted in a similar manner.

In the 6-methyl-substituted derivatives **6a-j**, however, the chemical shifts of the methylene protons in the piperidine ring are no longer equal while those of ring **C** still are. This indicates that the energies of the two half-chair conformers of ring **A** are different, and in solution one of them becomes predominant. Although the *equatorial* position is, in general, more favourable for a methyl group, in this conformer one must reckon with an unfavourable steric interaction between the methyl group and the neighbouring amide carbonyl in *peri* position. The favoured conformer can be determined by the investigation of the *CH*-6 signal. Although the rather high value of the chemical shift (δ 5.00 ± 0.1) indicates the presence of an *equatorial* proton, an unambiguous decision of this problem requires the determination of the spin-spin coupling constants with the 7-methylene protons. For this purpose the signal of the 6-methyl group was irradiated and the originally rather complex signal of the *CH*-6 proton simplified to a triplet with a splitting of 3 Hz. On this basis the *CH*-6 proton is *equatorial*, and, in accordance with the coupling constants $J_{7e,6a} \approx J_{7a,6e} = 3$ Hz, it is in *gauche* position to both *CH*-7 methylene protons. By comparison with analogous hydrogenated pyrido[1,2-*a*]-pyrimidin-4-one derivatives carrying a methylsubstituent in position 7 or 8, it can be concluded that the *axial* position of the 6-methyl group is due to the steric interaction with the amide carbonyl (22).

Figure 7

A pharmacological investigation of the new compounds described here was made by Prof. J. Knoll and co-workers (Semmelweiss Medical University, Budapest). During these studies it has appeared that several of the new derivatives possess considerable analgesic and outstanding morphine potentiating activity (23).

EXPERIMENTAL

The spectra were recorded on the following instruments: uv (in ethanol): Unicam SP 800; ir (potassium bromide): Unicam SP 200; pmr (deuteriochloroform): Perkin-Elmer R12 or JEOL PS-100 (δ TMS = 0). Melting points were determined on a Boetius apparatus and are uncorrected.

2,3-Tri-, Tetra-, Penta- and Hexamethylene-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**3a-v**).

Method A.

A mixture of 3.12 g. (0.02 mole) of ethyl 2-cyclopentanone-1-carboxylate, 2.16 g. (0.02 mole) of 2-amino-6-methylpyridine and 20 g. of PPA was stirred in a flask equipped with a stirrer and a

reflux condenser on a steam bath for 1.5 hours. The hot reaction mixture was diluted with 15-20 ml. of water, and neutralized with 10% sodium hydroxide with cooling. The separated crystals were filtered off and washed with a small amount of water. The obtained product (**3e**) was recrystallized from diisopropyl ether: pmr (deuteriochloroform): 7.25-7.50 (m, 2H, *H*-8, *H*-9), 6.61 (m, 1H, *H*-7), 3.08 (s, 3H, CH_3), 2.94 (m, 4H, $CH_2CH_2CH_2$), 2.15 (quintet, 2H, $CH_2CH_2CH_2$). The ir and uv data are shown in Table I; the physical and analytical data of **3e**, as well as of the compounds **3a-v**, prepared in the above manner, are summarized in Table II.

Method B.

To a mixture of 15.6 g. (0.1 mole) of ethyl 2-cyclopentanone-1-carboxylate and 10.8 g. (0.1 mole) of 2-amino-6-methylpyridine there was added a mixture of 28 ml. (46 g., 0.3 mole) of phosphoryl chloride and 7 g. of polyphosphoric acid: the reaction mixture was then heated at 120° in an oil bath for 3 hours, with stirring.

1. The reaction mixture was *cautiously* decomposed, with external cooling, by the addition of 50 ml. of water, and neutralized with 10% sodium hydroxide. The crystals were filtered off and washed with a small amount of water to obtain 14.6 g. (73%) of **3e**. The physical and spectroscopical properties of the product were identical with those of the product described above under Method A.

2. The reaction mixture was cooled to 70-80° and *cautiously* decomposed with 100 ml. of absolute ethanol. After standing for one night, the hydrochloride of the product (**3e**) was isolated as white crystals in 67% yield. The physical and analytical data of the hydrochlorides prepared in this manner are collected in Table II.

Method C.

The reaction of 2.82 g. (0.02 mole) of 2-oxo-1-cyclohexane-1-carboxamide with 1.88 g. (0.02 mole) of 2-aminopyridine in PPA, as described in Method A, gave **3b** in 46% yield: ir: ν max 2940, 1670, 1630, 1585, 1485 cm^{-1}; uv: λ max 331 (log ϵ = 4.01), 253 (4.04), 245.5 (3.10), 239 (3.08) nm; pmr (deuteriochloroform): 8.94 (dt, 1H, *H*-6, $J_{6,7}$ = 7.5 Hz, $J_{6,8}$ = $J_{6,9}$ = 1.5 Hz), 7.45-7.75 (m, 2H, *H*-8, *H*-9), 7.04 (m, 1H, *H*-7, $J_{7,8}$ = 6 Hz, $J_{7,9}$ = 2.5 Hz), 2.78 (m, 4H, CH_2-1', CH_2-4'), 1.88 (m, 4H, CH_2-2', CH_2-3'); lit. (12) ir: ν max 1670 cm^{-1}; uv (methanol): λ max 215 (4.20), 245 (4.10), 329 (4.04) nm; pmr (benzene-d_6): 8.85 (dt, 1H, *H*-6), 7.5 (m, 2H, *H*-8, *H*-9), 6.95 (m, 1H, *H*-7), 2.7, 1.85 (m, 8H, 4 x CH_2); lit. (13) ir: λ max 1680, 1635, 1580 cm^{-1}; pmr (deuteriochloroform): 7.8 (dt, 1H, *H*-6), 6.86-7.64 (m, 3H, *H*-7, *H*-8, *H*-9), 1.8, 2.8 (m, 8H, 4 x CH_2).

Method D.

1. A mixture of 0.02 mole of 2-aminopyridine hydroiodide, 0.03 mole of ethyl 2-cyclopentanone-1-carboxylate and 50 ml. of pyridine was refluxed for 6 hours. After evaporation of the solvent and the unchanged ketoester, the residue was crystallized from ethanol to give crystals of m.p. 212-214°, in a yield of 76%. Liberation of the base afforded 2,3-trimethylene-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**3a**).

Anal. Calcd. for $C_{11}H_{11}IN_2O$: C, 42.19; H, 3.54. Found: C, 41.82; H, 3.63.

2. Starting with 2-aminopyridine hydrobromide and ethyl 2-cyclopentanone-1-carboxylate, and using Method D/1 (reaction time: 8 hours, yield: 62%, m.p. 275-277°, from ethanol) and liberating the base, compound **3a** was obtained.

Anal. Calcd. for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15. Found: C, 49.80; H, 4.37.

3. 2,3-Trimethylene-4*H*-pyrido[1,2-*a*]pyrimidin-4-one hydrochloride (**3a**·HCl) was prepared from 2-aminopyridine hydrochloride and ethyl 2-cyclopentanone-1-carboxylate as described under D/1, with a reaction time of 16 hours and in 48% yield. The physical and spectral data of the product were identical with those of **3a**·HCl obtained according to Method B.

2,3-Trimethylene-7-amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**3v**).

Compound **3u** (2.31 g., 0.01 mole) (n = 1, 7-NO_2) and 3.9 g. (0.07 mole) of iron filings were suspended in 20 ml. of water. The mixture was stirred on a steam bath, and 3-4 ml. of concentrated hydrochloric acid was added dropwise over a period of 3 hours. The mixture was filtered, the filtrate neutralized with 10% sodium hydroxide, the separated fluffy crystals were aged by heating and extracted with 4 x 20 ml. of chloroform. The organic phase was dried and evaporated to give 0.72 g. (35%) of the yellow solid product, m.p. 260-264° (from ethanol). The analytical data of the compound are shown in Table II; ir: ν max 1660, 1640, 1470 cm^{-1}.

1,6-Dimethyl-2,3-trimethylene-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-1-ium Iodide (**4a**).

Compound **3a** (2.0 g., 0.01 mole) (n = 1, 6-CH_3) was dissolved in 25 ml. of absolute acetone, 7.1 g. (0.05 mole) of methyl iodide was added, and the mixture was heated for 10 hours at 100° in a sealed tube. The mixture was concentrated to 15 ml., and allowed to stand overnight. The separated crystals were filtered off (2.15 g., 67%, m.p. 225-228°). Recrystallization from ethanol gave glossy yellow crystals, m.p. 228-230°; ir: ν max 1725, 1610, 1490 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}IN_2O$: C, 45.63; H, 4.42. Found: C, 45.62; H, 4.43.

1,6-Dimethyl-2,3-trimethylene-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-1-ium Methyl Sulphate (**4b**).

Compound **3e** (4.0 g., 0.02 mole) (n = 1, 6-CH_3) was dissolved in 50 ml. of dry acetone, 2.52 g. (0.02 mole) of dimethylsulfate was added and the mixture heated under reflux for 16 hours. The solution was concentrated to about the half of its original volume, and a small amount of ether was added. Compound **4b** (4.96 g., 76%) was obtained. Recrystallization from ethanol-ether gave white crystals, m.p. 148-150°; ir: ν max 1710, 1620, 1500 cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}N_2O_5S$: C, 51.52; H, 5.56; N, 8.58. Found: C, 51.98; H, 5.58; N, 8.53.

2,3-Tetramethylene-1,4-dihydro-7-methyl-1,8-naphthyridin-4-one (**5b**).

The isomerization was carried out in 5% solution in paraffin oil. The solvent was heated to 300°, the corresponding pyrido-pyrimidine **3f** was added, and the solution was kept at this temperature for 20 minutes. After cooling, two volumes of petroleum ether were added, the crystals which separated were filtered off and washed several times with petroleum ether. The physical and analytical data of **5b** and of the naphthyridines **5a-f** prepared in the same manner are shown in Table III; their ir and uv data are listed in Table I.

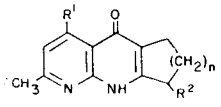
2,3-Tri-, Tetra-, Penta- and Hexamethylene-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**6a-i**).

Method A.

Compound **3e** (4.0 g., 0.02 mole) (n = 1, 6-CH_3) was dissolved in 50 ml. of ethanol and 5 g. of Raney nickel, which had been washed several times with dry ethanol, was added. The mixture

Table III

Melting Points and Analytical Data of Compounds **5a-f**

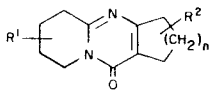


Compound No.	n	R^1	R^2	M.p., °C	Recrystallization Solvent	Yield, %	Molecular formula	Analyses Calcd. C	H	N	Found C	H	N
5a	1	H	H	>300	DMF (a)	92	$C_{12}H_{12}N_2O$	71.98	6.04	13.99	72.04	6.10	13.67
5b	2	H	H	>300	DMF (a)	88	$C_{13}H_{14}N_2O$	72.87	6.59	13.08	72.69	6.38	13.22
5c	3	H	H	>300	DMF (a)	90	$C_{14}H_{16}N_2O$	73.65	7.06	12.27	73.44	7.09	12.02
5d	4	H	H	>300	DMF (a)	90	$C_{15}H_{18}N_2O$	74.35	7.49	11.56	74.55	7.55	11.66
5e	1	CH_3	H	>300	DMF (a)	87	$C_{13}H_{14}N_2O$	72.87	6.59	13.08	73.00	6.65	12.95
5f	1	H	CH_3	275-277	Ethanol	89	$C_{13}H_{14}N_2O$	72.87	6.59	13.08	72.82	6.66	13.24

(a) Dimethylformamide.

Table IV

Melting Points, Analytical and Ir Spectral Data of Compounds **6a-j**



Compound No.	n	R^1	R^2	M.p., °C	Recrystallization Solvent	Molecular formula	Analyses Calcd. C	H	N	Found C	H	N	ir ν max cm^{-1}
6a	1	H	H	96-97	Petroleum Ether	$C_{11}H_{14}N_2O$	69.44	7.42	14.73	69.30	7.59	14.89	1660, 1515
6b(a)	2	H	H	172-173 (b)	*n*-Hexane	$C_{12}H_{16}N_2O$	70.56	7.90	13.72	70.45	8.22	13.74	2920, 1655, 1535
6c	3	H	H	159	*n*-Hexane	$C_{13}H_{18}N_2O$	71.52	8.31	12.83	71.49	8.22	12.94	2920, 1640, 1530
6d	4	H	H	110	Petroleum Ether	$C_{14}H_{20}N_2O$	72.33	8.68	12.06	72.22	8.64	12.09	1945, 1640, 1535
6e	1	6-CH_3	H	86-87	Petroleum Ether	$C_{12}H_{16}N_2O$	70.56	7.90	13.72	70.44	7.85	13.80	1670, 1505
6f	2	6-CH_3	H	128-130	*n*-Hexane	$C_{13}H_{18}N_2O$	71.52	8.31	12.83	71.42	8.31	12.72	2950, 1655, 1530
6g	3	6-CH_3	H	93-94	Petroleum Ether	$C_{14}H_{20}N_2O$	72.38	8.68	12.06	72.44	8.81	12.04	2910, 1640, 1525
6h	4	6-CH_3	H	70-71	Petroleum Ether	$C_{15}H_{22}N_2O$	73.13	9.00	11.37	73.04	9.10	11.32	2920, 1640, 1525
6i	1	6-CH_3	1'-CH_3	88-91	*n*-Hexane	$C_{13}H_{18}N_2O$	71.52	8.31	12.83	71.41	8.42	12.90	2940, 1660, 1510
6j	1	6-CH_3	2'-*t*-Bu	98-100	Ethyl Ether	$C_{16}H_{24}N_2O$	73.80	9.29	10.76	73.76	9.34	10.76	2960, 1670, 1515

(a) After recrystallization from ethanol-ether the hydrochloride forms white crystals, m.p. 185-195°. (b) Lit. (21) m.p. 168-170°; ir: ν max 1660 cm^{-1}.

was hydrogenated at room temperature and atmospheric pressure. After the absorption of the calculated amount of hydrogen (4 hours) the hydrogenation process stopped abruptly. After filtering off the Raney nickel, the filtrate was evaporated to dryness to obtain 2,3-trimethylene-6-methyl-6,7,8,9-tetrahydro-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one (**6e**) in a quantitative yield; pmr (deuteriochloroform): δ 5.01 (m, 1H, H_e-6, $J_{6e,7e} = J_{6e,7a} = 3$ Hz), 2.98 (m, 2H. CH_2-9), 2.85 (t, 4H, CH_2-1′, CH_2-3′), 2.10 (quintet, 2H, CH_2-2′). 1.98 (m, 4H, CH_2-7, CH_2-8), 1.37 (d, 3H, CH_3-6).

Method B.

When aplladium-on-charcoal containing 10% of metal was used instead of Raney nickel (1.0 g. of palladium-on-charcoal for 0.02 mole of the substrate in 50 ml. of ethanol), 6 hours were necessary for completion of the hydrogenation. The yields were, also in this case, quantitative for each compound.

The physical and spectral data of compounds **6e-j** prepared by methods A and B were the same. Their analytical and ir data are shown in Table IV.

Method C.

2-Iminopiperidine hydrochloride (2.7 g., 0.02 mole) was treated with an equivalent amount of sodium ethoxide in 20 ml. of dry ethanol, and the mixture was allowed to stand for one hour. The precipitated sodium chloride was filtered off. The resulting solution of the base was mixed with 3.4 g. (0.02 mole) of ethyl 2-cyclohexanone-1-carboxylate, and the mixture was refluxed for one hour. The solvent was evaporated and the residue crystallized from acetone-*n*-hexane furnishing **6b** in 74% yield; the physical and spectroscopic data of the product were identical with those of the same compound prepared according to Method A or B: pmr (deuteriochloroform): δ 3.96 (t, 2H, CH_2-6), 2.92 (t, 2H. CH_2-9), 2.5-2.67 (m, 4H, CH_2-1′, CH_2-4′), 1.7-2.1 (m, 8H. 4 x CH_2). Similar pmr chemical shift values are given in the literature (21), without making assignments of the bands.

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