SATURATED HETEROCYCLES, XXI*
SYNTHESIS OF 2,3-TRIMETHYLENE- AND TETRAMETHYLENE--4-OXO-PYRIDO[1,2-*a*]PYRIMIDINE-7-, 8- AND 9-CARBOXYLIC ACID DERIVATIVES WITH POTENTIAL PHARMACOLOGICAL ACTIVITY

By

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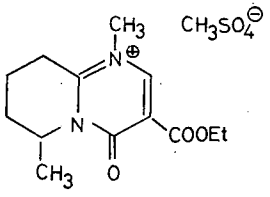
From substituted 2-aminopyridines and ethyl-(2-cyclopentanone- or 2-cyclohexanonecarboxylates), 7-, 8- or 9-carboxylic acid derivatives of 2,3-trimethylene- and tetramethylene-4-oxo-pyrido-[1,2-*a*]pyrimidine were synthesized using polyphosphoric acid or phosphortrichloride-oxide and polyphosphoric acid mixture as condensing agent.

The 4-oxo-pyrido[1,2-*a*]pyrimidines, their synthesis, chemical and pharmacological behaviour have been the subject of our extensive study for more then ten years [1, 2]. The compounds excelled in analgetic activity. One of them, *"Probon"* (**1**) has since been introduced in Hungary, as a new analgetic.



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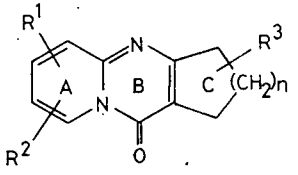

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* For previous parts of this Series, see: Part XI: F. Fülöp, I. Hermecz, Z. Mészáros, Gy. Dombi, G. Bernáth: J. Heterocyclic Chem. **16**, 457 (1979); Part XII: G. Bernáth, F. Fülöp, Gy. Jerkovich, P. Sohár: Acta Chim. (Budapest) **101**, ... (1979), in press; Part XIII: P. Sohár, L. Gera, G. Bernáth: Organic Magnetic Resonance, in press; Part XIV: L. Gera, G. Bernáth, P. Sohár: Acta Chim. (Budapest), in press; as part XV is regarded: B. Ribár, A. Petrović, Gy. Göndös, G. Bernáth: Cryst. Struct. Comm. **8**, 671 (1979). The parts XXXIX—XLIII of the Series „Stereochemical Studies", G. Bernáth, A. Kálmán *et al.*, Cryst. Struct. Comm. **9**, (1980), in press are also considered to be Parts XVI—XX of the Series „Saturated Heterocycles".

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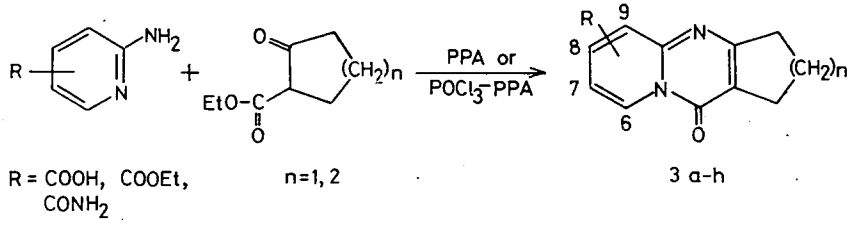
In our previous publication [3] we reported the synthesis and some chemical reactions of the 2,3-polymethylene-derivatives (**2**) of the 4-oxo-pyrido[1,2-*a*]pyrimidines. The substituents of **2** ($n=1-4$) were: alkyl, hydroxyl, nitro, and halogen. According to the expectation, most of the derivatives had considerable, and some of them significant analgetic activity [4]. In the case of $n=2$, compounds **2** comprize the pyrido[2,1-*b*]quinazoline ring, which is a frequent and essential structural element of some plant alkaloides [5].



As a continuation of the previous work, here we give an account on some new derivatives of **2**, in which the pyridine ring bears carboxy-group substituent. These compounds may possibly also be of biological interest. Recently some pyrido[2,1-*b*]quinazolin-carboxylic acids, with aromatic "C" ring, have been reported [6–8] to exhibit significant antiallergic — first of all antiasthmatic — effect, and they showed activity — in contrast to *"Intal"* — also after oral administration.

In the synthesis we started from the corresponding substituted 2-amino-pyridine and alicyclic ethyl β-keto-carboxylates (the ring size of the esters was 5 and 6). The carboxy-substituted 2-amino-pyridines, not available commercially, were prepared by known methods [9–11]. The condensation reaction was carried out by either the method of SHUR and ISRAELSTAM [12], using polyphosphoric acid (PPA), or by the method reported by MÉSZÁROS *et al.* [1], using phosphortrichloride-oxyde and polyphosphoric acid mixture ($POCl_3$—PPA) as condensing agent. Independent of the size of the alicyclic ring of the δ-ketocarboxylate, both methods were appropriate for the preparation of the pyrido-pyrimidines, although the PPA method proved to give better yields and purer products in this case. The yields are shown in Table I.

The resulting pyrido[1,2-*a*]pyrimidines (**3a-h**) are insoluble in water. The esters dissolve readily, while the carboxylic acids and the amides are rather insoluble in common organic solvents. The structures were proved by elementar analysis and by spectroscopic methods. The data of the elementar analysis and the UV and IR characteristics are given Tables I and II, respectively.

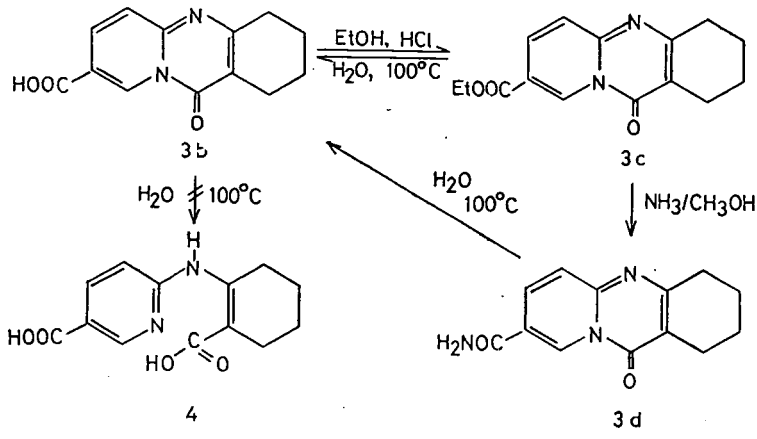
Some reactions of the carboxyl group of the 7-substituted 2,3-tetramethylene derivatives were carried out. The **3c** ester and the **3d** amide were hydrolysed into the **3b** carboxylic acid in a 2% aqueous hydrochloric acid solution at 100° C. The **3d** carboxylic acid was converted into ester in good yield, in boiling ethanolic hydrochloric acid solution and the carboxamide **2d** was formed quantitatively from the ester on the effect of methanolic ammonia solution.

Table I

Physical characteristics and analytical data for compounds **3a-h**

Compound	R	*n*	Formula, Molecular weight	M. p. (°C) Solvent for recrystallization	Analysis (%) Cald./Found			Yield (%	
					C	H	N	PPA	$POCl_3$-PPA
3a	7-COOH	1	$C_{12}H_{10}N_2O_3$ 230.22	325[a] DMF	62.60 62.74	4.38 4.46	12.17 12.06	55	40
3b	7-COOH	2	$C_{13}H_{12}N_2O_3$ 244.24	255-258 ethanol	63.92 63.84	4.95 5.00		51	44
3c	7-COOEt	2	$C_{15}H_{16}N_2O_3$ 272.29	100-102 ether	66.16 66.20	5.92 6.02		67	49[b]
3d	7-$CONH_2$	2	$C_{13}H_{13}N_3O_2$ 243.26	313-315 DMF	64.18 64.22	5.39 5.61	17.28 17.01	41	
3e	8-COOEt	2	$C_{15}H_{16}N_2O_3$ 272.29	92-93 ether	66.16 66.24	5.92 5.81		81	52[b]
3f	9-COOH	1	$C_{12}H_{10}N_2O_3$ 230.22	189-193[c] ethanol	62.60 62.56	4.38 4.44	12.17 12.30	48[b]	
3g	9-COOH	2	$C_{13}H_{12}N_2O_3$ 244.24	202-204 ethanol	63.92 63.96	4.96 4.96	11.47 11.59	46	
3h	9-COOEt	2	$C_{15}H_{16}N_2O_3$ 272.29	143-144 ethanol	66.16 66.20	5.92 5.87		63	

[a] Under decomposition
[b] The reaction mixture was treated with ethanol
[c] Lit. [13] m.p.: 191-3 °C, yield: 58%



The compounds **3a-h** are weak bases. The hydrochlorides could only be prepared from the ester derivatives, while those of the carboxylic acids and the amides — though they could be prepared —, the parent bases were deliberated under the conditions of the recrystallization.

Table II

UV and IR characteristics of compounds **3**

Compound	R	*n*	UV Absorption Maxima (log ε) [nm]		IR ν_{max} (cm^{-1})
3a	7-COOH	1	344 (—)	236 (—)	1720, 1695
3b	7-COOH	2	344 (2.99)	235 (3.28)	1725, 1695
3c	7-COOEt	2	345 (4.08)	238 (4.43)	1730, 1685, 1500
3d	7-$CONH_2$	2	344 (—)	235 (—)	1685, 1495, 1450, 1415
3e	8-COOEt	2	370 (3.89)	264 (4.07)	1730, 1670
3f*	9-COOH	1	335 (3.97)	268 (4.14) 262 (4.13)	1725, 1695, 1585
3g	9-COOH	2	330 (3.93)	260 (5.05)	1730, 1695, 1595, 1490
3h	9-COOEt	2	336 (4.00)	259 (4.08)	1735, 1670, 1485

* Lit [13] IR (in $CDCl_3$): *v* 1700—2500 (broad *s*), 1720-1670 (broad *s*), 1575 (*s*), 1530 (*s*) 1500—1415 (broad *s*) cm^{-1}.

The pharmacological behaviour of the compounds is under investigation [14].

Experimental

Melting points were determined on a Boetius apparatus, and are uncorrected. The IR spectra were taken in KBr pills with a Unicam SP 200 spectrometer. The UV spectra were recorded in ethanolic solution on a Unicam SP 800 spectrophotometer.

2,3-Tetramethylene-4-oxo-pyrido[1,2-a]pyrimidine-7-carboxylic acid (**3b**)

a) *in PPA:*

3.4 g (20 mmol) of 2-Carbethoxycyclohexanone and 2.76 g (20 mmol) of 6-amino-nicotinic acid were stirred and heated in 20 g of polyphosphoric acid, on a water bath for 1.5 hrs. Than the hot reaction mixture was carefully diluted with 10–20 ml of water, and neutralized under cooling with a 10% aqueous ammonia solution. After 1 hr of standing, the resulting crystals were collected, washed with water and dried. The product (2.5 g, 51%) was crystallized from ethanol.

Compounds **3a, c-h** were obtained similarly. For yields and melting points see Table I.

b) *in $POCl_3$—PPA mixture:*

2-Carbethoxycyclohexanone (3.4 g, 20 mmol) and 6-amino-nicotinic acid (2.76 g, 20 mmol) were heated and stirred in a mixture of phosphortrichloride-oxyde (5.6 ml, 60 mmol) and polyphosphoric acid (1.4 g) on a water bath for 1.5 hrs. After the cease of the hydrochloric acid evolution, ice-cold water was dropwise added to the hot reaction mixture, and it was afterwards neutralized with 10% aqueous ammonia solution. After 1 hr of standing the resulting crystals were collected, washed with water and dried. The product (2.15 g, 44%) was crystallized from ethanol. The product showed no melting point depression with the sample obtained in the PPA ring closure.

Compounds **3a, c, e** were prepared similarly. For yields see Table I.

Ethyl 2,3-tetramethylene-4-oxo-pyrido[1,2-a]pyrimidine-7-carboxylate (**3c**)

1 g of 2,3-Tetramethylene-4-oxo-pyrido[1,2-*a*]pyrimidine-7-carboxylic acid (**3b**) was refluxed for 3 hrs in a 20% ethanolic hydrochloric acid solution. The solution was evaporated, the crystalline residue was dissolved in 20 ml of water, and neutralized with saturated aqueous sodium hydrocarbonate solution. The resulting yellow crystals (0.92 g, 82%) were crystallized from ether, m.p.: 99–101 °C. The product did not show melting point depression with the ester **3c** obtained in the PPA or $POCl_3$—PPA ring closure.

2,3-Tetramethylene-4-oxo-pyrido[1,2-a]pyrimidine-7-carboxamide (**3d**)

1 g of Ethyl 2,3-tetramethylene-4-oxo-pyrido[1,2-*a*]pyrimidin-7-carboxylate (**3c**) was dissolved in 10 ml of saturated methanolic ammonia solution. The amide (**3f**) started to precipitate in 10 minutes. The reaction mixture was left overnight. The crystals were collected (0.84 g, 94%), and purified by crystallization from dimethyl-formamide to obtain pale yellow crystals, m.p.: 312–5 °C. The product did not show melting point depression with the corresponding amide obtained by the PPA ring closure.

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НАСЫЩЕННЫЕ ГЕТЕРОЦИКЛЫ. XXI. СИНТЕЗ 2,3-ТРИМЕТИЛЕН- И ТЕТРАМЕТИЛЕН-4-ОКСО-ПИРИДО[1,2-*a*]ПИРИМИДИНО-7-, 8- И 9 - КАРБОКСИЛЬНЫХ ПРОИЗВОДНЫХ С ВЕРОЯТНОЙ ФАРМАКОЛОГИЧЕСКОЙ АКТИВНОСТЬЮ

Ф. Фюлеп, Г. Бернат, И. Гермец и З. Месарош

Из замещенных 2-аминопиридинов и этил-(2-циклопентанон- или 2-циклогексанон карбоксилатов), 7-, 8- или 9-карбоксильных производных были синтетизированы 2,3-триметилен- и тетраметилен-4-оксо-пиридо[1,2-*a*]пиримидины с применением в качестве конденсирующих агентов полифосфорной кислоты или смеси фосфортрихлорного окисла и полифосфорной кислоты.

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