Chemistry of Heterocyclic Compounds, Vol. 38, No. 7, 2002

EXOTIC AMINO ACIDS.

6*. SYNTHESIS OF SUBSTITUTED 4-OXO-4H-PYRIDO[1,2-*a*]PYRIMIDINES

I. Ravina[1], D. Zicane[1], M. Petrova[1], E. Gudriniece[1], and U. Kalejs[2]

2-Pyridylaminomethyleneisopropylidenemalonates, prepared from ethoxymethyleneisopropylidenemalonate and 2-aminopyridines, form 4-oxo-4H-pyrido[1,2-a]pyrimidines at their melting points and are separated from the reaction mixture by sublimation.

Keywords: 2-aminopyridines, 4-oxo-4H-pyrido[1,2-*a*]pyrimidines, 2-pyridylaminomethylene-isopropylidenemalonates, ethoxymethyleneisopropylidenemalonate.

Among pyridopyrimidines there are compounds which possess antitumour [2], antibacterial [3], diuretic [4], and antiviral [5] properties.

We previously reported [6] on the synthesis of 4-oxo-7R-4H-pyrido[1,2-*a*]pyrimidines from 2-pyridylamino- and 5-methyl-2-pyridylaminomethyleneisopropylidenemalonates by melting them. This method of obtaining derivatives of pyridopyrimidines had not been described in the literature at that time. However the authors of paper [7] obtained pyrazolo[1,5-*a*]pyrimidines by refluxing 5-pyrazolylaminomethylene-isopropylidenemalonates in nitrobenzene. We note that our attempts to use similar conditions for the synthesis of pyrido[1,2-*a*]pyrimidines **4a-j** were not crowned with success. Complex mixtures of substances which were difficult to separate were obtained.

In this work we have studied in more detail the behavior of compounds **3a-j** on heating with the objective of using our method [6] for the synthesis of various pyridopyrimidines.

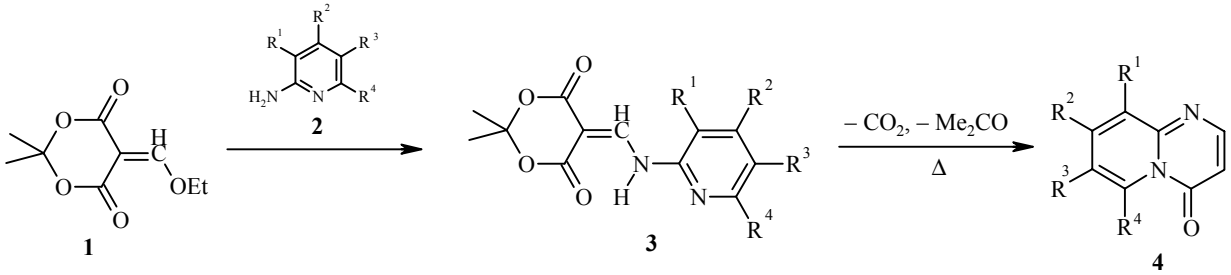
We obtained compounds **3a-j** by the method described elsewhere [8] from ethoxymethyleneisopropylidenemalonate **1** and 2-aminopyridines **2a-j** in ethanol solution at room temperature for 2-24 h.

When the pyridylaminomethylenemalonates **3a-j** were heated to their melting points the dioxane ring opened, acetone was evolved, followed by decarboxylation and cyclization to give the substituted 4-oxo-4H-pyrido[1,2-*a*]pyrimidines **4a-j**. Compounds **4a-g** sublimed (yields 47-74%) and required no further purification. Compound **4h** sublimed along with the starting material **3h** and was separated by extraction with hexane (29% yield). Compounds **4i,j** were obtained in poor yields (**4i** – 24, **4j** – 21%) and their preparation by this method is of no interest.

* For part 5 see [1].

[1] Riga Technical University, Riga LV-1048; e-mail: gudr@ktf.rtu.lv. [2] BAPEKS Ltd., Riga LV-1048, Latvia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, 945-946, July, 2002. Original article submitted April 20, 2000.

 0009-3122/02/3807-0836$27.00



2–4 a $R^1 = R^2 = R^4 = H$, $R^3 = Cl$; **b** $R^1 = R^2 = R^4 = H$, $R^3 = Br$; **c** $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$; **d** $R^2 = R^4 = H$, $R^1 = R^3 = Cl$; **e** $R^2 = R^4 = H$, $R^1 = R^3 = Br$; **f** $R^2 = R^3 = R^4 = H$, $R^1 = Me$; **g** $R^1 = R^3 = R^4 = H$, $R^2 = Me$; **h** $R^1 = R^2 = R^3 = H$, $R^4 = Me$; **i** $R^1 = R^3 = R^4 = H$, $R^2 = Et$; **j** $R^2 = R^3 = H$, $R^1 = Et$, $R^4 = Me$

TABLE 1. Characteristics of 2-Pyridylaminomethyleneisopropylidene-malonates **3a-j**

Com-pound	mp, °C	^{1}H NMR spectrum, ppm. (*J*, Hz)	Yield, %
3a	193-194	1.67 (6H, s, $2CH_3$); 7.03 (1H, d, *J* = 9, C_5H_3N); 7.72 (1H, dd, *J* = 9, *J* = 2, C_5H_3N); 8.32 (1H, d, *J* = 2, C_5H_3N); 9.30 (1H, d, *J* = 14, =CH); 11.27 (1H, br. d, *J* = 14, NH)	95
3b	192-193 192-192.4 [9]	1.69 (6H, s, $2CH_3$); 7.01 (1H, d, *J* = 9, C_5H_3N); 7.82 (1H, dd, *J* = 9, *J* = 2, C_5H_3N); 8.41 (1H, d, *J* = 2, C_5H_3N); 9.28 (1H, d, *J* = 13, =CH); 11.3 (1H, br. d, *J* = 13, NH)	96 76 [9]
3c	237-238	1.72 (6H, s, $2CH_3$); 7.82 (1H, d, *J* = 9, C_5H_4N); 8.67 (1H, dd, *J* = 9, *J* = 2, C_5H_4N); 9.25 (1H, d, *J* = 14, =CH); 9.27 (1H, d, *J* = 2, C_5H_4N); 11.61 (1H, br. d, *J* = 14, NH)	47
3d	216-220	1.65 (6H, s, $2CH_3$); 7.83 (1H, d, *J* = 2, C_5H_2N); 8.27 (1H, d, *J* = 2, C_5H_2N); 9.2 (1H, d, *J* = 14, =CH–); 11.66 (1H, br. d, *J* = 14, NH)	94
3e	207-208	1.69 (6H, s, $2CH_3$); 7.96 (1H, d, *J* = 2, C_5H_2N); 8.32 (1H, d, *J* = 2, C_5H_2N); 9.22 (1H, d, *J* = 13, =CH) 11.7 (1H, br. d, *J* = 13, NH)	80
3f	185-186 186-187 [9]	1.69 (6H, s, $2CH_3$); 2.36 (3H, s, CH_3); 7.07 (1H, dd, *J* = 8, *J* = 6, C_5H_3N); 7.56 (1H, dd, *J* = 8, *J* = 1.5, C_5H_3N); 8.27 (1H, dd, *J* = 6, *J* = 1.5, C_5H_3N); 9.49 (1H, d, *J* = 13, =CH–) 11.63 (1H, br. d, *J* = 13, NH)	75 56 [9]
3g	197-198	1.78 (6H, s, $2CH_3$); 2.38 (3H, s, CH_3); 6.86 (1H, d, *J* = 1.5, C_5H_3N); 7.1 (1H, d, *J* = 5, C_5H_3N); 8.25 (1H, d, *J* = 5, C_5H_3N); 9.33 (1H, d, *J* = 14, =CH); 11.18 (1H, br. d, *J* = 14, NH)	48
3h	153-156 155-160 [9]	1.72 (6H, s, $2CH_3$); 2.49 (3H, s, CH_3); 6.85 (1H, d, *J* = 8, C_5H_3N); 7.03 (1H, d, *J* = 8, C_5H_3N); 7.63 (1H, t, *J* = 8, C_5H_3N); 9.41 (1H, d, *J* = 14, =CH); 11.31 (1H, br. d, *J* = 14, NH)	75 45 [9]
3i	123-125	1.18 (3H, t, *J* = 7, CH_3); 1.67 (6H, s, $2CH_3$); 2.61 (2H, q, *J* = 7, CH_2); 6.82 (1H, d, *J* = 1.5, C_5H_3N); 6.93 (1H, d, *J* = 5, C_5H_3N); 8.18 (1H, d, *J* = 5, C_5H_3N); 9.35 (1H, d, *J* = 14, =CH); 11.13 (1H, br. d, *J* = 14, NH)	53
3j	162-166 162-165 [9]	1.27 (3H, t, *J* = 7, CH_3); 1.72 (6H, s, $2CH_3$); 2.45 (3H, s, CH_3); 2.62 (2H, q, *J* = 7, CH_2); 6.96 (1H, d, *J* = 8, C_5H_4N); 7.49 (1H, d, *J* = 8, C_5H_4N); 9.52 (1H, d, *J* = 13, =CH–); 11.7 (1H, br. d, *J* = 13, =CH–)	75 58 [9]

TABLE 2. Characteristics of the Substituted 4-Oxo-4H-pyrido[1,2-*a*]pyrimidines Synthesized, **4a-j**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	Yield, %
		C	H	N	Hal			
4a	$C_8H_5ClN_2O$	53.41 / 53.21	2.52 / 2.79	15.34 / 15.51	19.15 / 19.63	121-123	6.35 (1H, d, *J* = 7, 3-H); 7.55 (2H, m, 9-H, 8-H); 8.15 (1H, d, *J* = 7, 2-H); 9.0 (1H, d, *J* = 2, 6-H)	50
4b	$C_8H_5BrN_2O$	42.40 / 42.70	2.41 / 2.22	12.71 / 12.45	35.65 / 35.51	127-130	6.33 (1H, d, *J* = 7, 3-H); 7.46 (1H, d, *J* = 9, 9-H); 7.66 (1H, dd, *J* = 9, *J* = 2, 8-H); 8.24 (1H, d, *J* = 7, 2-H); 9.04 (1H, d, *J* = 2, 6-H)	62
4c	$C_8H_5N_3O_3$	50.12 / 50.27	2.73 / 2.64	21.99 / 21.98		152-154	6.42 (1H, d, *J* = 7, 3-H); 7.61 (1H, d, *J* = 9, 6-H); 8.23 (1H, d, *J* = 7, 2-H); 8.34 (1H, dd, *J* = 9, *J* = 2, 7-H); 9.90 (1H, d, *J* = 2, 9-H)	47
4d	$C_8H_4Cl_2N_2O$	44.43 / 44.68	2.24 / 1.87	13.20 / 13.03	33.10 / 32.97	128-129	6.49 (1H, d, *J* = 7, 3-H); 7.79 (1H, d, *J* = 2, 8-H); 8.29 (1H, d, *J* = 7, 2-H); 8.91 (1H, d, *J* = 2, 6-H)	74
4e	$C_8H_4Br_2N_2O$	31.56 / 31.61	1.31 / 1.33	9.29 / 9.22	53.02 / 52.58	185-188	6.38 (1H, d, *J* = 7, 3-H); 8.18 (1H, d, *J* = 2, 8-H); 8.29 (1H, d, *J* = 7, 2-H); 9.06 (1H, d, *J* = 2, 6-H)	52
4f	$C_9H_8N_2O$	67.13 / 67.49	5.38 / 5.03	17.35 / 17.49		110-113	2.56 (3H, s, CH_3); 6.34 (1H, d, *J* = 7, 3-H); 6.89 (1H, t, *J* = 7.5, 7-H); 7.52 (1H, dd, *J* = 7.5, *J* = 1.5, 8-H); 8.23 (1H, d, *J* = 7, 2-H); 8.89 (1H, dd, *J* = 7.5, *J* = 1.5, 6-H)	59
4g	$C_9H_8N_2O$	67.70 / 67.49	4.92 / 5.03	17.52 / 17.49		136-141	2.42 (3H, s, CH_3); 6.27 (1H, d, *J* = 7, 3-H); 6.82 (1H, dd, *J* = 8, *J* = 2, 7-H); 7.35 (1H, d, *J* = 2, 9-H); 8.18 (1H, d, *J* = 7, 2-H); 8.89 (1H, d, *J* = 8, 6-H)	50
4h	$C_9H_8N_2O$	67.33 / 67.49	4.91 / 5.03	17.62 / 17.49		111-114	3.01 (3H, s, CH_3); 6.16 (1H, d, *J* = 7, 3-H); 6.6 (1H, m, 8-H); 7.33 (2H, m, 9-H, 7-H); 7.99 (1H, d, *J* = 7, 2-H)	29
4i	$C_{10}H_{10}N_2O$	69.08 / 68.95	5.66 / 5.79	15.90 / 16.08		73-74	1.23 (3H, t, *J* = 7, CH_3); 2.71 (2H, q, *J* = 7, CH_2); 6.29 (1H, d, *J* = 7, 3-H); 6.95 (1H, dd, *J* = 8, *J* = 2, 7-H); 7.41 (1H, d, *J* = 2, 9-H); 8.18 (1H, d, *J* = 7, 2-H); 8.91 (1H, d, *J* = 8, 6-H)	24
4j	$C_{11}H_{12}N_2O$	70.02 / 70.19	6.39 / 6.43	16.72 / 14.88		57-61	1.22 (3H, t, *J* = 7, CH_3); 2.77 (2H, q, *J* = 7, CH_2); 2.91 (3H, s, CH_3); 6.2 (1H, d, *J* = 7, 3-H); 6.6 (1H, d, *J* = 7.5, 7-H); 7.17 (1H, d, *J* = 7.5, 8-H); 8.03 (1H, d, *J* = 7, 2 -H)	21

The composition of the compounds synthesized was confirmed by the results of elemental analysis, and their structures by the ^{1}H NMR spectra, in which the proton signal of all the fragments of the molecules resonated in their characteristic regions.

EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ or DMSO-d_6 solutions with HMDS as internal standard were recorded with a Bruker WH90/DS instrument (90 MHz).

The purity of the synthesized compounds were monitored by TLC on Silufol strips with the following solvent systems: chloroform–methanol–glacial acetic acid, 9:1:1 (**3b-e,j**), ethyl acetate (**3f-i, 4b-j**), and chloroform (**3a, 4a,b**).

Characteristics of the compounds synthesized are given in Tables 1 and 2.

2-Pyridylaminomethyleneisopropylidenemalonates (3a-j). A solution of ethoxyisopropylidenemalonate **1** (0.005 mol) [7] in ethanol (10 ml) at ~20°C was added with stirring to an equimolar quantity of the corresponding 2-aminopyridine **2a-j** dissolved in ethanol. In the case of **3i** the reaction mixture was heated for 1 h at 50°C. The precipitate was filtered off after 2-3 h (**3a-e**) or 24 h (**3f-j**). In the case of **3i**, water (100 ml) was added to the reaction mixture. Compound **3h** was recrystallized from ethanol, **3i** from 1:2 acetonitrile–water. Compounds **3a-g,j** were chromatographically homogeneous and did not require recrystallization.

Substituted 4-Oxo-4H-pyrido[1,2-*a*]pyrimidines (4a-j). Compounds **3a-g** (0.002 mol) were melted in a porcelain cup, closed with a glass funnel. The sublimates were chromatographically homogeneous for compounds **4a-g**. Compounds **4h-j** were isolated from the fused mixture with hexane.

REFERENCES

1. D. R. Zicane, Z. F. Tetere, I. A. Rijkure, M. V. Petrova, E. Yu. Gudriniece, and U. O. Kalejs, *Khim. Geterotsikl. Soedin.,* 903 (2000).
2. H. Akimoto, T. Miwa, and K. Otsu, Jap. Pat. 04,235,986; *Chem. Abstr.,* **118**, 213101 (1993).
3. B. Hurlbert and B. Valenti, *J. Med. Chem.,* **11**, 708 (1968).
4. H. Parish, P. Gilliom, W. Purcell, R. Browne, R. Spirk, and H. White, *J. Med. Chem.,* **25**, 98 (1982).
5. D. Bouzard, *Anitbiotics and Antiviral Compounds*, VCH (Weinheim), 186 (1993).
6. D. R. Zicane, I. T. Ravina, Z. F. Tetere, I. A. Rijkure, E. J. Gudrinece, and U. O. Kalejs, *Khim. Geterotsikl. Soedin.*, 857 (2000).
7. J. Quiroga, A. Hormoza, B. Insuasty, C. Saitz, C. Jullian, and A. Canete, *J. Heterocycl. Chem.,* **35**, 61 (1998).
8. G. Bihlmayer, G. Derflinger, J. Derkosch, and O. Polansky, *Monatsh. Chem.,* **98**, 564 (1967).
9. Sterling Drug, Brit. Pat. 1147759; *Chem. Abstr.,* **71**, 70125 (1969).