4-ETHOXYMETHYLENE-2-PHENYL-5(4*H*)-OXAZOLONE AS A SYNTHON FOR THE SYNTHESIS OF SOME FUSED PYRIMIDINES

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Abstract - Treatment of 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone with nitrogen-containing heterocycles, having amino group in *ortho* position to the ring nitrogen, leads to the corresponding 4-(arylamino-methylene)-2-phenyl-5(4*H*)-oxazolones, which can be further converted into different fused pyrimidinones. The (*Z*)-structure of the oxazolone exocyclic double bond has been determined on the basis of ^{13}C nmr spectroscopy.

The ethoxy group in 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (2) has been substituted with different nucleophiles.[1-3] These conversions took place under different reaction conditions, neutral, acidic or basic. Tsuge and Noguchi have described the transformations of oxazolone (2) with 1,3-binucleophiles such as 2-aminopyridines, 2-aminothiazole and 2-amino-

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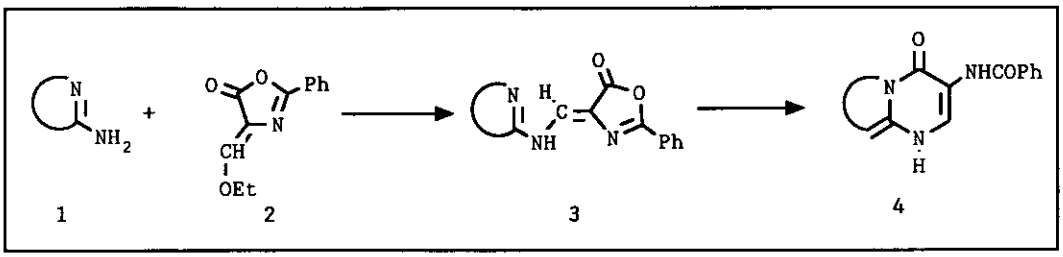
Dedicated to Prof. Dr. Edward C. Taylor, Professor of Princeton University, on the occasion of his 70th birthday.

pyrimidine into the corresponding aminomethyleneoxazolones and fused pyrimidinones.[4]

In this paper we report transformations of some aminoheterocycles (**1**) with ethoxymethyleneoxazolone (**2**) into 4-(arylaminomethylene)-2-phenyl-5(4*H*)-oxazolones of type **5** and fused pyrimidinones of type **4** (or eventually tautomeric form). We also describe two structure determinations of the exocyclic oxazolone double bonds. In continuation of our work,[5] we prepared several 4-(arylaminomethylene)-2-phenyl-5(4*H*)-oxazolones (**5a-i**), starting *from different aminoheterocycles and compound* (**2**) *in ethanolic solutions in* high yields. These compounds can exist in several tautomeric forms and in two types of geometric isomers. They were studied by ^{13}C nmr spectroscopy in order to get some data about the configurations of the exocyclic oxazolone double bonds. We used the method in which the magnitude of the coupling constant between the oxazolone carbon 5-C and vicinal proton of the exocyclic CH group was examined.[5,6] 5-Methyl-1*H*-pyrazolyl derivative (**5b**) and 1*H*-pyrazolo[3,4-*b*]pyridinyl derivative (**5i**) were examined by this method. In DMSO-d_6 at 80 °C we found the following vicinal coupling constants: for **5b** 2.6 Hz at 166.9 ppm and for **5i** 2.7 Hz at 167.0 ppm. These values are typical for (*Z*)-isomers and are in accordance with our previous results[5] and with the X-ray analysis of a compound of this type.[7] The NH proton in a compound of type **5** could be localized as shown in the structure **5**, where in ^1H nmr CHNH fragment appears as two doublets (see **5i**: J=12.2 Hz). When the signals of this fragment are covered with the signals of the other groups and when they are singlets or broad singlets (instead of doublets), the participation of the tautomeric form having NH proton on the heterocyclic ring can not be excluded.

On the other hand, on heating in acetic acid or in a mixture of pyridine and triethylamine, the starting compounds (**1**) and (**2**) have been directly converted into the fused pyrimidinones (**6-13**), which can also be formed from the intermediates (**5**) either thermally without any solvent (on the



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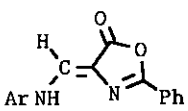

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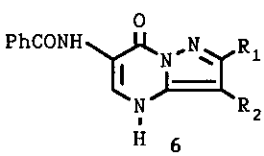
	Ar
5a	1*H*-Pyrazolyl-3
b	5-Methyl-1*H*-pyrazolyl-3
c	4-Ethoxycarbonyl-1*H*-pyrazolyl-3
d	5-Methylthio-1*H*-1,2,4-triazolyl-3
e	4-Ethoxycarbonylmethyl-2-thiazolyl

	Ar
5f	5-Chloro-2-pyridinyl
g	1*H*-Indazolyl-3
h	2-Benzothiazolyl
i	1*H*-Pyrazolo[3,4-*b*]pyridin-3-yl



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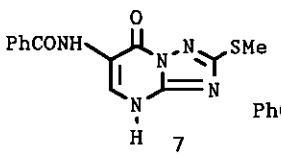
	R_1	R_2
6a	H	H
b	Me	H
c	H	CO_2Et



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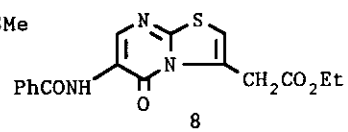

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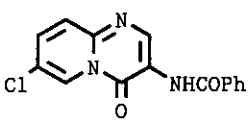

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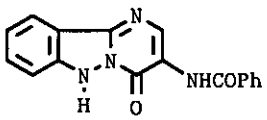

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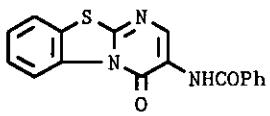

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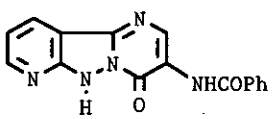

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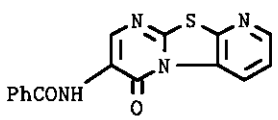

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Kofler micro hot stage) or on heating in the previously mentioned solutions (as shown in the case of pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine derivative (12). All reactions were followed by tlc. We would like to note that in the case of 3-amino-5-methylthio-1*H*-1,2,4-triazole two products might be formed, namely the [1,2,4]-triazolo[1,5-*a*]pyrimidine derivative (7) and isomeric *N*-[3-methylthio-5-oxo-5,8-dihydro-1,2,4-triazolo[4,3-*a*]-pyrimidin-6-yl]benzamide. Based on the known results,[8,9] under our conditions the formation of the compound (7) seems to be more plausible.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. Nmr spectra were recorded with a JEOL JNM FX90Q, Varian EM360L, and Varian VXR 300 instruments, using TMS as internal standard. Mass spectra were recorded with a VG-Analytical AutoSpecEQ instrument. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. Tlc was carried out on Fluka silica gel tlc cards. Compound (2),[10] 3-aminoindazol,[11] 3-amino-pyrazolo[3,4-*b*]pyridine,[12] and 2-aminothiazolo[4,5-*b*]pyridine[13] were prepared as described in the literature. All other reagents were used as received from commercial sources.

General procedure for the synthesis of 4-(arylaminomethylene)-2-phenyl-5(4*H*)-oxazolones (5a-i). A mixture of the corresponding amino compound (1 mmol) and 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone (2) (217 mg, 1 mmol) in 2-4 ml of dry ethanol was heated under reflux for 1 h (in the case of **5b** 3 h of heating; in the case of **5c** and **5i** 4 h at room temperature). After evaporation of the solvent 1 ml of ethanol was added to the residue. Upon cooling the solid product was taken by filtration and washed with a small amount of ethanol.

The following compounds were prepared by this method:

5a: From 3-amino-1*H*-pyrazole and **2** in 90% yield. mp about 250 °C conversion into **6a** (from EtOH); ^{1}H nmr (90 MHz, DMSO-d_6) δ 6.16 (1H, d, J=2.2 Hz, 4′-H), 7.53-7.60 (3H, m, Ph), 7.70 (1H, d, J=2.2 Hz, 5′-H), 7.96 (3H, m, CH, Ph), 10.9 (1H, br s, NH), 12.56 (1H, br s, NH). Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.18; H, 3.85; N, 22.07.

5b: From 3-amino-5-methyl-1*H*-pyrazole and **2** in 87% yield. mp about 250 °C conversion into **6b** (EtOH/DMF); ^{1}H nmr (60 MHz, DMSO-d_6) δ 2.23 (3H, s, Me), 5.97 (1H, s, 4′-H), 7.60 (3H, m, Ph), 8.00 (3H, m, CH, Ph), 10.93 (1H, br s, NH), 12.33 (1H, br s, NH). Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.56; H, 4.48; N, 20.92.

5c: From 3-amino-5-ethoxycarbonyl-1*H*-pyrazole and **2** in 66 % yield. mp about 250 °C conversion into **6c** (EtOH/DMF); ^{1}H nmr (60 MHz, DMSO-d_6) δ 1.37 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.35 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 7.63 (3H, m, Ph), 7.87-8.12 (3H, m, CH, Ph), 8.37 (1H, s, 5′-H), 10.3 (1H, br, NH), 13.4 (1H, br s, NH). Anal. Calcd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.49; H, 4.29; N, 17.02.

5d: From 3-amino-5-methylthio-1*H*-1,2,4-triazole and **2** in 82% yield. mp 223-225 °C with conversion into **7** (EtOH/DMF); ^{1}H nmr (90 MHz, DMSO-d_6) δ 2.63 (3H, s, Me), 7.58 (3H, m, Ph), 7.87-8.02 (3H, m, CH, Ph). Anal. Calcd for $C_{13}H_{11}N_5O_2S$: C, 51.82; H, 3.68; N, 23.24. Found: C, 51.83; H, 3.67; N, 23.08.

5e: From 2-amino-4-(ethoxycarbonylmethyl)thiazole and **2** in 82% yield. mp 169-171 °C (EtOH/DMF); ^{1}H nmr (60 MHz, DMSO-d_6) δ 1.22 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 3.72 (2H, s, CH_2), 4.13 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 7.08 (1H, s, 5′-H), 7.62 (3H, m, Ph), 7.92-8.17 (3H, m, CH, Ph), 12.07 (1H, br s, NH). Exact Mass Calcd for $C_{17}H_{15}N_3O_4S$: 357.0783. Found: 357.0773.

5f: From 2-amino-5-chloropyridine and **2** in 77% yield. mp 224-228 °C (MeOH/DMF); ^{1}H nmr (60 MHz, DMSO-d_6) δ 7.37 (1H, d, J=9 Hz, 3′-H), 7.62

(3H, m, Ph), 7.93 (1H, dd, J=9 Hz and 2.6 Hz, 4'-H), 7.93-8.13 (2H, m, Ph), 8.33 (1H, br s, CH), 8.42 (1H, d, J=2.6 Hz, 6'-H). Anal. Calcd for $C_{15}H_{10}ClN_3O_2$: C, 60.11; H, 3.36; N, 14.02. Found: C, 60.31; H, 3.08; N, 13.74.

5g: From 3-amino-1*H*-indazole and **2** in 93% yield. mp about 250 °C conversion into **10** (EtOH/DMF); ^{1}H nmr (90 MHz, DMSO-d_6) δ 7.13 (1H, deg ddd, 6'-H), 7.40-7.63 (5H, m, 4'-H, 5'-H, 3H of Ph), 7.98-8.24 (4H, m, 7'-H, CH, 2H of Ph), 11.46 (1H, br, NH), 12.74 (1H, br s, NH); ms (m/z) 304 (M^+, 38%). Anal. Calcd for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41. Found: C, 66.85; H, 3.92; N, 18.66.

5h: From 2-aminobenzothiazole and **2** in 55% yield. mp 216-219 °C (EtOH/DMF); ^{1}H nmr (90 MHz, DMSO-d_6) δ 7.18-8.13 (10H, m, Ph, 4'-H, 5'-H, 6'-H, 7'-H, CH), 12.2 (1H, br s, NH). Anal. Calcd for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08. Found: C, 63.37; H,3.42; N,13.07.

5i: From 3-amino-1*H*-pyrazolo[3,4-*b*]pyridine and **2** at room temperature in 77% yield. mp above 200 °C conversion into **13** (EtOH/DMF); ^{1}H nmr (60 MHz, DMSO-d_6) δ 7.23 (1H, dd, J=8 and 5 Hz, 5'-H), 7.62 (3H, m, Ph), 8.05 (2H, m, Ph), 8.15 (1H, d, J=12.2 Hz, CH), 8.55-8.77 (2H, two deg dd, 4'-H, 6'-H), 11.68 (1H, br d, J=12.2 Hz, NH), 13.37 (1H, br s, NH). Anal Calcd for $C_{16}H_{11}N_5O_2$: C, 62.95; H, 3.63; N, 22.94. Found: C, 63.23; H, 3.69; N, 22.94.

General procedure for the synthesis of fused pyrimidines (6-13). A mixture of the corresponding amino compound (2 mmol) and 4-ethoxymethylene-2-phenyl-5(4*H*)-oxazolone **(2)** (434 mg, 2 mmol) in 4 ml of acetic acid (or in a mixture of 4 ml of pyridine and 0.2 ml of triethylamine, Py/NEt_3) was heated under reflux for 4-20 h (see bellow). After evaporation of the solvent 2 ml of ethanol was added to the residue. Upon cooling the solid product was taken by filtration and washed with a small amount of ethanol.

The following compounds were prepared by this method:

***N*-[7-Oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-yl]benzamides (6):**

a: From 3-amino-1*H*-pyrazole and **2** in AcOH after 4 h in 32% yield; in Py/NEt_3, 20 h, 61% yield. mp above 300 °C (EtOH/DMF); ^1H nmr (90 MHz, DMSO-d_6) δ 6.23 (1H, d, J=2 Hz, 3-H), 7.55 (3H, m, Ph), 7.90-8.06 (3H, m, 2-H, Ph), 8.35 (1H, s, 5-H), 9.59 (1H, br s, NH). Anal. Calcd for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.58; H, 3.95; N, 22.25.

b: From 3-amino-5-methyl-1*H*-pyrazole and **2**; AcOH, 4 h, 62%; in Py/NEt_3 after 20 h a mixture of compounds **6b** and **5b** is formed in 82% overall yield. mp above 350 °C (DMF); ^1H nmr (60 MHz, DMSO-d_6, 150 °C) δ 2.32 (3H, s, Me), 6.00 (1H, s, 3-H), 7.57 (3H, m, Ph), 8.01 (2H, m, Ph), 8.42 (1H, s, 5-H), 9.00 (1H, s, NH). Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.45; H, 4.47; N, 20.99.

c: From 3-amino-5-ethoxycarbonyl-1*H*-pyrazole and **2**; Py/NEt_3, 4h, 67%. mp about 300 °C (decomp.) (EtOH/DMF); ^1H nmr (90 MHz, DMSO-d_6) δ 1.34 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 4.34 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 7.59 (3H, m, Ph), 7.99 (2H, m, Ph), 8.29 (1H, s) and 8.44 (1H, s) (2-H, 5-H), 9.65 (1H, s, NH). Anal. Calcd for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.68; H, 4.31; N, 16.88.

***N*-[2-Methylthio-7-oxo-4,7-dihydro-[1,2,4]-triazolo[1,5-*a*]pyrimidin-6-yl]-benzamide (7):** From 3-amino-5-methylthio-1*H*-1,2,4-triazole and **2**; Py/NEt_3, 15 h, 66%. mp above 300 °C (DMF); ^1H nmr (60 MHz, DMSO-d_6) δ 2.63 (3H, s, CH_3), 7.60 (3H, m, Ph), 8.02 (2H, m, Ph), 8.43 (1H, s, 5-H), 9.70 (1H, s, NH); ms (m/z) 301 (M^+, 34%). Anal. Calcd for $C_{13}H_{11}N_5O_2S$: C, 51.82; H, 3,68; N,23,24. Found: C, 51,96; H, 3,49; N, 23,32.

Ethyl 6-Benzoylamino-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-3-acetate (8): From 2-amino-4-(ethoxycarbonylmethyl)thiazole and **2**; AcOH, 4 h, 77%; Py/NEt_3, 6 h, 70%. mp 194.5-195.5 °C (DMF); ^1H nmr (60 MHz, DMSO-d_6) δ 1.17 (3H, t, J=7 Hz, $C\underline{H}_3CH_2O$), 4.12 (2H, q, J=7 Hz, $CH_3C\underline{H}_2O$), 4.25 (2H, s, CH_2), 7.45 (1H, s, 2-H), 7.64 (3H, m, Ph), 8.06 (2H, m, Ph), 8.68 (1H, s, 7-H), 9.58 (1H, s, NH). Anal. Calcd for $C_{17}H_{15}N_3O_4S$: C, 57.13; H, 4.23; N, 11.76.

Found: C, 57.27; H, 3.96; N, 11,71.

***N*-[7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl]benzamide (9):**

From 2-amino-5-chloropyridine and **2**; AcOH, 4 h, 80%; Py/NEt_3, 20 h, 60%. mp 213-214 °C (DMF); ^1H nmr (60 MHz, DMSO-d_6) δ 7.60 (3H, m, Ph), 7.83-8.15 (4H, m, 8-H, 9-H, Ph), 9.05 and 9.07 (2H, d covered with s, 6-H, 2-H), 9.83 (1H, s, NH). Exact Mass Calcd for $C_{15}H_{10}ClN_3O_2$: 299.0462. Found: 299.0468.

***N*-[4-Oxo-4,6-dihydropyrimido[1,2-*b*]indazol-3-yl]benzamide (10):**

From 3-amino-1*H*-indazole and **2**; AcOH, 5 h, 79%; in Py/NEt_3 after 20 h a mixture of compounds **10** and **5g** is formed in 74% overall yield. mp above 300 °C (DMF); ^1H nmr (90 MHz, DMSO-d_6, 150 °C) δ 7.23 (1H, m), 7.50-7.62 (5H, m), 7.93-8.13 (3H, m), 8.80 (1H, s, 2-H), 9.15 (1H, broad s, NH). Exact Mass Calcd for $C_{17}H_{12}N_4O_2$: 304.0960. Found: 304.0964.

***N*-[4-Oxo-4*H*-pyrimido[2,1-*b*]benzothiazol-3-yl]benzamide (11):**

From 2-aminobenzothiazole and **2**; AcOH, 4 h, 82%; Py/NEt_3, 8 h, 84%. mp 228-230 °C (EtOH/DMF); ^1H nmr (90 MHz, DMSO-d_6) δ 7.51-7.67 (5H, m, 7-H, 8-H, Ph), 7.96-8.15 (3H, m, 9-H, Ph), 8.69 (1H, s, 2-H), 8.95 (1H, dd, J=7.1 and 2.9 Hz, 6-H), 9.62 (1H, br s, NH). Anal. Calcd for $C_{17}H_{11}N_3O_2S$: C, 63.54; H, 3.45; N, 13.08. Found: C, 63.07; H, 3.41; N, 13.10.

***N*-[4-Oxo-4,6-dihydropyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidin-3-yl]-benzamide (12):** From 3-amino-1*H*-pyrazolo[3,4-*b*]pyridine and **2**; AcOH, 4 h, 47%; Py/NEt_3, 20 h, 22%. From compound **5i** in Py/NEt_3 after 5 h of heating, 28%. mp above 300 °C (AcOH/EtOH); ^1H nmr (90 MHz, DMSO-d_6, 150 °C) δ 7.07 (1H, dd, J=7.7 and 5.1 Hz, 9-H), 7.51 (3H, m, Ph), 7.95 (2H, m, Ph), 8.50-8.65 (2H, m, 8-H, 10-H), 8.89 (1H, s, 2-H), 9.11 (1H, br, NH). Anal. Calcd for $C_{16}H_{11}N_5O_2$: C, 62.95; H, 3.63; N, 22.94. Found: C, 63.13; H, 3.77; N, 22.78.

***N*-[6-Oxo-6*H*-pyrido[3',2':4,5]thiazolo[3,2-*a*]pyrimidin-7-yl]benzamide (13):**

From 2-aminothiazolo[5,4-*b*]pyridine and **2**; AcOH, 5 h, 68%. mp 215-217 °C (EtOH/DMF); ^1H nmr (60 MHz, DMSO-d_6) δ 7.55-7.87 (4H, m, 3-H, Ph), 8.08 (2H, m, Ph), 8.72 (1H, dd, J=5 and 1.6 Hz, 2-H), 8.77 (1H, s, 8-H), 9.15

(1H, dd, J=8.4 and 1.6 Hz, 4-H), 9.67 (1H, br s, NH). Anal. Calcd for $C_{16}H_{10}N_4O_2S$: C, 59.62; H, 3.13; N, 17.38. Found: C, 59.48; H, 3.09; N, 17.40.

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