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SYNTHESIS OF FUSED SYSTEMS CONTAINING AN ANGULAR NITROGEN ATOM FROM SUBSTITUTED 2-BENZYL-4-HYDRAZINOPYRIDIMINES

G. G. Danagulyan[1], L. G. Sahakyan[1], and G. A. Panosyan[2]

The condensation of substituted 2-benzyl-4-hydrazinopyrimidines with phenylpyruvic acid gave the corresponding hydrazones, which cyclize upon the action of $POCl_3$ to give derivatives of pyrimido[6,1-c][1,2,4]-triazine. The substituted 2-benzylpyrimidinylhydrazides of some carboxylic acids react with $POCl_3$ to give 1,2,4-triazolo[4,3-c]pyrimidines. The reaction of 7-benzyl-5-methyl-1-phenyl-1,2,4-triazolo[2,3-c]pyrimidine with sodium ethylate leads to rearrangement and formation of 7-benzyl-5-methyl-2-phenyl-1,2,4-triazolo[2,3-c]pyrimidine.

Keywords: hydrazides, hydrazone, Dimroth rearrangement, pyrimidine, pyrimido[6,1-*c*][1,2,4]triazine, 1,2,4-triazolo[2,3-*c*]pyrimidine, 1,2,4-triazolo[4,3-*c*]pyrimidine.

Compounds containing fused pyrimidine systems and an angular nitrogen atom hold interest as potential analgetics [1, 2], broncholytics, and respiratory stimulators [3] as well as antitumor drugs [4, 5]. On the other hand, the presence of a bridging nitrogen has a significant effect on the reactivity of such systems [6, 7] and generates interest for a study of their chemical properties.

Considerable biological activity is also characteristic for derivatives of 2-benzylpyrimidine [8, 9]. We have synthesized a series of hydrazides and hydrazones of substituted benzylpyrimidines displaying membrane-altering, cholinolytic, and histamine-blocking activity [10] and showed that several hydrazones have herbicidic and fungicidic activity, in particular, relative to the suppression of *Botrytis cinerea*.

In a continuation of a study of fused pyrimidine systems [11-13], we have synthesized a series of new triazolo[4,3-*c*]pyrimidines and pyrimido[6,1-*c*][1,2,4]triazines containing a benzyl fragment at the pyrimidine ring. The condensation of substituted 2-benzyl-4-hydrazinopyrimidines **1a** and **1b** with phenylpyruvic acid and of hydrazinopyrimidine **1a** with ketone **4** gave the corresponding hydrazones. Heating hydrazones **2a** and **2b** with $POCl_3$ at reflux led to cyclization to give derivatives of pyrimido[6,1-*c*][1,2,4]triazine **3a** and **3b**. Cyclization does not occur in glacial acetic acid.

Heating hydrazone **5** with $POCl_3$ at reflux gave a chloro derivative but did not lead to the expected closure of the triazine ring. This result probably should be attributed to the existence of this compound largely in diazo form **6** and absence (or low concentration) of tautomers **6a** and **6b** (Scheme 1). This behavior would explain the ^1H NMR spectrum, in which we find a methine quartet at 2.65 ppm, methyl doublet at 1.05 ppm, and singlets for the methylene and methyl fragments of the side chain.

[1] Yerevan Institute of the National Economy, 375025 Yerevan, Republic of Armenia; e-mail: ysine@ysine.am. [2] Center for the Study of Molecular Structure, National Academy of Sciences of the Republic of Armenia, 375025 Yerevan, Republic of Armenia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 225-229, February, 2000. Original article submitted September 21, 1999.

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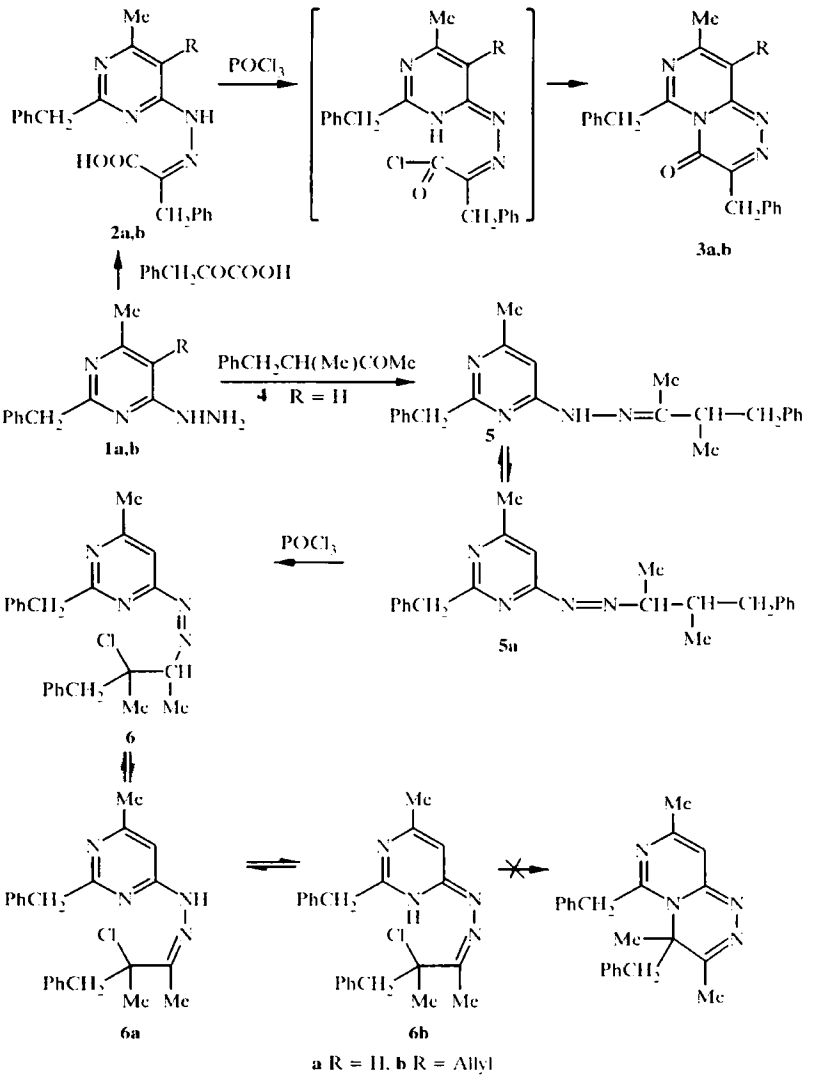
Scheme 1



The reaction of pyrimidinylhydrazides of carboxylic acids with $POCl_3$ gave 1-substituted 5-methyl-7-benzyl-1,2,4-triazolo[4,3-*c*]pyrimidines **8a-d**. Heating 1-phenyl derivative **8c** with sodium ethylate at reflux led to a Dimroth rearrangement to give 7-benzyl-5-methyl-2-phenyl-1,2,4-triazolo[2,3-*c*]pyrimidine **9c**. As noted in our previous work [13], an attempt to achieve the analogous isomerization of 1-isopropyl derivative **8b** led to destructive hydration of the molecule and isolation of intermediate adduct **10b** (Scheme 2, Table 1).

EXPERIMENTAL

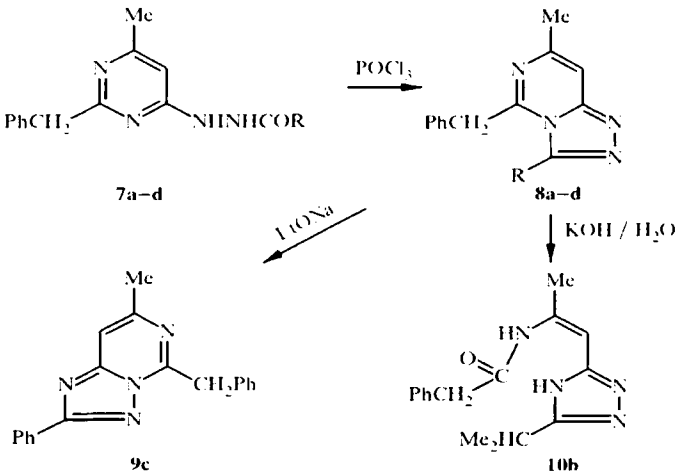
The ^{1}H NMR spectra were taken on a Varian Mercury 300 spectrometer using the US CRDF RESC 17-5 program. Double resonance was used to assign the signals. Silufol UV-254 plates were used for thin-layer chromatography and iodine vapor was used for development.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f (benzene–acetone, 3:1)	Yield, %
		C	H	N			
1b	$C_{15}H_{18}N_4$	70.71 / 70.84	6.98 / 7.13	22.17 / 22.03	131-132	0.64*	92
2a	$C_{21}H_{20}N_4O_2$	69.71 / 69.98	5.41 / 5.59	15.89 / 15.55	258-259		90
2b	$C_{23}H_{24}N_4O_2$	71.69 / 71.98	6.30 / 6.04	13.81 / 13.99	219-220		60
3a	$C_{21}H_{18}N_4O$	73.53 / 73.67	5.09 / 5.30	16.23 / 16.36	108-110	0.35	46
3b	$C_{24}H_{22}N_4O$	75.19 / 75.37	5.98 / 5.80	14.51 / 14.65	95-96	0.57	40
5	$C_{23}H_{26}N_4$	77.20 / 77.06	7.08 / 7.31	15.47 / 15.63		0.62	90
6	$C_{23}H_{25}ClN_4$	70.09 / 70.31	6.25 / 6.41	14.14 / 14.26	180	0.42	25
8a	$C_{15}H_{16}N_4$	71.28 / 71.40	6.25 / 6.39	22.08 / 22.20	78-80	0.87	51
8b	$C_{16}H_{18}N_4$	71.93 / 72.15	6.04 / 6.18	21.17 / 21.04	77-78	0.56	63
8c	$C_{19}H_{16}N_4$	75.69 / 75.98	5.29 / 5.37	18.89 / 18.65	130-131	0.73	50
8d	$C_{19}H_{15}N_5O_2$	65.81 / 66.08	4.21 / 4.38	20.04 / 20.28	115-117	0.35	58
9c	$C_{19}H_{16}N_4$	75.71 / 75.98	5.41 / 5.37	18.91 / 18.65	76-77	0.56	80

* Benzene–acetone, 1 : 1.

Scheme 2



a R = Et, **b** R = $CHMe_2$, **c** R = Ph, **d** R = C_6H_4-*m*-NO_2

5-Allyl-2-benzyl-4-hydrazino-6-methylpyrimidines (1b). A mixture of 5-allyl-2-benzyl-4-methyl-6-chloropyrimidine (51.7 g, 0.2 mol) and 85% hydrazine hydrate (18.5 g, 0.31 mol) in ethanol (30 ml) was heated at reflux for 10 h. The mixture was evaporated to dryness at reduced pressure and cooled. The residue was washed with water and hexane, filtered, and recrystallized from carbon tetrachloride. ^{1}H NMR ($CDCl_3$): 2.33 (3H, s, 4-CH_3); 3.25 (2H, d, J = 5.5 Hz, $\underline{CH_2}$–CH=CH_2); 3.93 (2H, s, $\underline{CH_2}$Ph); 5.01 (1H, d, J = 10.0 Hz, $\underline{CH_2}$=CH); 5.04 (1H, d, J = 16.8 Hz, $\underline{CH_2}$=CH); 5.83 (1H, ddt, J_1 = 5.5, J_2 = 10.0, J_3 = 16.8 Hz, $\underline{CH}$=CH_2); 7.23-7.40 (5H, m, Ph); 12.4 ppm (1H, br. s, NH).

Preparation of 2-Benzyl-6-methyl-4-pyrimidinylhydrazones of α-Keto Acids (2a, 2b). A mixture of hydrazinopyrimidine **1** (5 mmol) and phenylpyruvic acid (5 mmol) in ethanol (25 ml) was heated at reflux for 4-5 h [14]. After cooling, the crystalline precipitate was filtered off, washed with 2 ml cold ethanol, and dried. ^{1}H NMR spectrum for compound **2a** (DMSO-d_6): 2.38 (3H, s, 4-CH_3); 3.78 (2H, s, $\underline{CH_2}$–C=N); 3.98 (2H, s, 2-$\underline{CH_2}$PH); 6.91 (1H, s, 5-H); 7.1-7.29 (11H, m, $(C_6H_5)_2$ and NH); 12.3 ppm (1H, br. s, CO_2H). ^{1}H NMR spectrum for compound **2b** (DMSO-d_6): 2.4 (3H, s, 4-CH_3); 3.37 (2H, d, J = 5.7 Hz, $\underline{CH_2}$–CH=CH_2); 3.84 (2H, s, $\underline{CH_2}$–C=N); 4.05 (2H, s, 2-$\underline{CH_2}$Ph); 5.01 (1H, d, J = 15.8 Hz, $\underline{CH_2}$–CH); 5.04 (1H, d, J = 9.5 Hz, $\underline{CH_2}$=CH); 5.84 (1H, ddt, J_1 = 15.8, J_2 = 9.5, J_3 = 5.7 Hz, $\underline{CH}$=CH_2); 7.08-7.38 (10H, m, $(C_6H_5)_2$); 13.5 ppm (1H, br. s, CO_2H).

9-Allyl-6-benzyl-8-methyl-4H-pyrimido[6,1-*c*][1,2,4]triazin-4-one (3b). A mixture of 5-allyl-2-benzyl-6-methyl-4-pyrimidinylhydrazone of phenylpyruvic acid **2b** (0.8 g, 2 mmol) and $POCl_3$ (10 ml) was left at room temperature for 15-20 h. The reaction mixture was then carefully poured onto ground ice (50 g), neutralized by adding aq. KOH, and extracted with chloroform. The extract was dried over magnesium sulfate. The solvent was distilled off. The residue was cooled. Hexane was added and the crystalline precipitate was filtered off and dried. ^{1}H NMR ($CDCl_3$): 2.51 (3H, s, 4-CH_3); 3.6 (2H, d, J = 5.5 Hz); $\underline{CH_2}$–CH=CH_2); 4.18 (2H, s, 3-CH_2Ph); 4.35 (2H, s, 6-$\underline{CH_2}$PH); 5.04 (1H, d, J = 9.0 Hz, $\underline{CH_2}$=CH); 5.05 (1H, d, J = 18.0 Hz, $\underline{CH_2}$=CH); 5.88 (1H, ddt, J_1 = 5.5, J_2 = 9.0, J_3 = 18.0 Hz, $\underline{CH}$=CH_2); 7.05-7.37 ppm (10H, m, Ph_2).

6-Benzyl-8-methyl-4H-pyrimido[6,1-*c*][1,2,4]triazin-4-one (3a) was obtained by heating hydrazone **2a** (0.75 g, 2 mmol) in $POCl_3$ (10 ml) at reflux for 10 h and work-up as in the previous procedure. ^{1}H NMR ($CDCl_3$): 2.51 (3H, s, 4-CH_3); 4.18 (2H, s, CH_2); 4.38 (2H, s, CH_2); 6.83 (1H, s, 5-H); 7.21-7.37 ppm (10H, m, Ph_2).

2-Benzyl-6-methyl-4-pyrimidylhydrazone of 3-Methyl-4-phenyl-2-butanone (5). A mixture of hydrazinopyrimidine **1a** (1.1 g, 5 mmol) and 3-methyl-4-phenyl-2-butanone **4** (0.8 g, 5 mmol) [15] in ethanol (10 ml) was heated at reflux for 10 h. Ethanol was distilled off to dryness. The viscous product was washed with hexane to give 1.65 g (90%) of compound **5**. ^{1}H NMR ($CDCl_3$): 1.08 (3H, d, J = 6.1 Hz, $\underline{CH_3}$CH); 1.11 (3H, d, J = 6.5 Hz, $\underline{CH_3}$CHCH$_2$Ph); 2.08 (3H, s, 4-CH_3); 2.5-2.8 (1H, m, $\underline{CH}$(CH_3)CH_2Ph); 2.75 (2H, d, J = 5.8 Hz, CH(CH_3)$\underline{CH_2}$Ph); 2.95 (1H, dq, J = 6.1, J = 3.1 Hz, $\underline{CH}CH_3$); 4.11 (2H, s, 2-CH_2Ph); 6.84 (1H, s, 5-H); 7.13-7.35 ppm (10H, m, Ph_2).

2-Benzyl-4-methyl-6-[(3'-methyl-4'-phenyl-3'-chlorobutane-2')azo]pyrimidine (6). A mixture of hydrazone **5** (0.8 g, 2.2 mmol) and $POCl_3$ (7 ml) was heated on a water bath for 5 h. After cooling, finely ground ice (20 g) was added. The mixture was neutralized by adding aq. KOH and extracted with chloroform. The extract was dried over magnesium sulfate. The solvent was evaporated and hexane was added to the residue. The crystalline precipitate was filtered off. ^{1}H NMR spectrum (DMSO-d_6): 1.05 (3H, d, J = 6.0 Hz, $\underline{CH_3}$CH); 1.25 (3H, s, CH_3CCl); 2.45 (3H, s, 4-CH_3); 2.53 (2H, s, $\underline{CH_2}$CCl); 2.65 (1H, q, J = 6.0 Hz, $\underline{CH}CH_3$); 4.08 (2H, s, 2-$\underline{CH_2}$Ph); 6.58 (1H, s, 5-H); 7.21-7.39 ppm (10H, m, Ph_2).

1-Substituted 5-Methyl-7-benzyl-1,2,4-triazolo[4,3-*c*]pyrimidines (8a-d). A mixture of 2-benzyl-6-methyl-4-pyrimidinylhydrazide of carboxylic acid **7** (2.5 mmol) [10] and $POCl_3$ (15 ml) was heated at reflux for 8-10 h. Excess of $POCl_3$ was distilled off. Finely ground ice was added and the mixture was neutralized by adding aq. KOH. Crystalline **8c** and **8d** were filtered off and recrystallized from aq. ethanol (**8c**) or heated in ethanol with activated charcoal (**8d**). After neutralization, **8a** and **8b** were extracted with chloroform. The extract was dried over magnesium sulfate. The solvent was distilled off and hexane was added to the residue. The crystalline precipitate was filtered off and recrystallized from hexane. ^{1}H NMR spectrum for compound **8a** ($CDCl_3$): 1.51 (3H, t, J = 6.7 Hz, $CH_2\underline{CH_3}$); 2.50 (3H, s, 5-CH_3); 3.33 (2H, q, J = 6.7 Hz, $\underline{CH_2}CH_3$); 4.5 (2H, s, CH_2Ph); 7.31-7.50 ppm (6H, m, Ph and 4-H). ^{1}H NMR for compound **8b** ($CDCl_3$): 1.45 (6H, d, J = 6.4 Hz, $\underline{Me_2}$CH); 2.55 (3H, s, 5-CH_3); 3.25 (1H, m, J = 6.4 Hz, $\underline{CH}Me_2$); 4.6 (2H, s, $\underline{CH_2}$Ph); 7.28-7.55 ppm (6H, m, Ph and 4-H). ^{1}H NMR of **8c** ($CDCl_3$): 2.59 (3H, s, 5-CH_3); 4.71 (2H, s, CH_2); 7.3-7.6 and 8.33 ppm (11H, m, $\underline{Ph}$, $\underline{Ph}CH_2$, and 4-H). ^{1}H NMR spectrum for compound **8d** (DMSO-d_6): 2.28 (3H, s, 5-CH_3); 3.93 (2H, s, $\underline{CH_2}$PH); 7.1-7.35 (5H, m, Ph); 7.18 (1H, s, 4-H); 7.78 (1H, t, J = 5.7 Hz, 5'-H); 8.38 (2H, dd, J = 5.7 Hz, 4'-H and 6'-H); 8.8 ppm (1H, s, 2'-H).

7-Benzyl-5-methyl-2-phenyl-1,2,4-triazolo[2,3-*c*]pyrimidine (9c). A sample of compound **8c** (0.2 g, 1 mmol) in ethanolic sodium ethylate obtained by adding sodium (0.02 g) to absolute ethanol (3 ml) was heated at reflux for 3 h and neutralized by adding ethereal hydrogen chloride. The mixture was filtered and evaporated to

dryness. Then, hexane (5 ml) was added to the residue. The crystalline precipitate was filtered off and recrystallized from hexane. ^{1}H NMR spectrum (CD_2Cl_2): 2.38 (3H, s, 5-CH_3); 3.72 (2H, s, $\underline{CH_2}$Ph); 7.23 (1H, s, 4-H); 7.2-7.55 ppm (10H, m, $\underline{Ph}$ and $CH_2\underline{Ph}$).

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