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Utilization of Organoselenium Compounds. II.[1] Reaction of Fused Isoselenazoles with Alkylamines

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A facile conversion of the methyl group of 5-amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (**1**) or 4-aminoantipyrine (**5**) to an alkyliminomethyl group by isoselenazole ring formation followed by reaction with alkylamines was carried out. 7-Oxo-6-phenyl-6*H*-isoselenazolo[4,3-*d*]pyrimidine (**2**), which was obtained from **1** and selenium dioxide, was reacted with alkylamines, such as *n*-propylamine, isopropylamine and 3-methoxypropylamine, to give 6-alkyliminomethyl-5-amino-3-phenyl-4(3*H*)-pyrimidinones (**3a—d**) in 47—58% yields. Treatment of **3a—d** with silica gel gave 5-amino-6-formyl-3-phenyl-4(3*H*)-pyrimidinone (**4**) in 91% yield. Similarly the reaction of 5,6-dihydro-4-methyl-6-oxo-5-phenyl-4*H*-pyrazolo[4,3-*c*]isoselenazole (**6**) with alkylamines gave 3-alkyliminomethyl-4-amino-1-phenyl-3-pyrazolin-5-ones (**7a—f**) in 50—97% yields.

Keywords——isoselenazole; isoselenazolo[4,3-*d*]pyrimidine; pyrazolo[4,3-*c*]isoselenazole; alkylamine; 4-aminoantipyrine; pyrimidine; selenium dioxide

Recently, chemical and biological applications of organoselenium compounds have developed considerably.[2] Studies on the syntheses of selenium containing heterocycles have also been carried out in our laboratory, and some biologically interesting compounds and reactions have been reported.[1,3] As a continuation of our work, this paper deals with a facile conversion of the methyl group of 5-amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone[4] (**1**) or 4-aminoantipyrine[5] (**5**) to an alkyliminomethyl group by isoselenazole ring formation followed by reaction with alkylamines.

Synthesis of 7-oxo-6-phenyl-6*H*-isoselenazolo[4,3-*d*]pyrimidine (**2**) by the reaction of **1** with selenium dioxide in dioxane was reported by us previously.[3a] It is said that organoselenium comounds are susceptible to nucleophilic attack on the selenium atom, usually resulting in cleavage of the weak C–Se bond.[2a] Thus, it appeared to be interesting to examine the reaction of **2** with alkylamines. Treatment of **2** with primary alkylamines, such as *n*-propylamine, isopropylamine, *n*-butylamine, and 3-methoxypropylamine in ethanol under reflux for 7—24 h gave 6-alkyliminomethyl-5-amino-3-phenyl-4(3*H*)-pyrimidinones (**3a—d**) in 47—58% yields. These products were purified by recrystallization from ethanol. An attempt to purify **3** by column chromatography on silica gel gave 5-amino-6-formyl-3-phenyl-4(3*H*)-pyrimidinone (**4**) in 91% yield. Similarly, the reaction of 5,6-dihydro-4-methyl-6-oxo-5-phenyl-4*H*-pyrazolo[4,3-*c*]isoselenazole[6] (**6**) with alkylamines gave 3-alkyliminomethyl-4-amino-1-phenyl-3-pyrazolin-5-ones (**7a—f**) in 50—97% yields. The infrared (IR) spectra of all these compounds (**3a—d, 4, 7a—f**) showed NH_2 absorptions, and elemental analyses and mass spectra were consistent with the assigned structures (Tables I and II). Recrystallization of **7a—f** from ethanol gave analytically pure samples. However, treatment of **7a—f** with silica gel gave reddish intractable glutinous substances, from which only a trace amount of a compound of mp 137—139 °C [$m/z=217$ (M^+)], possibly 4-amino-3-formyl-2-methyl-1-phenyl-3-pyrazolin-5-one (**8**), was obtained.

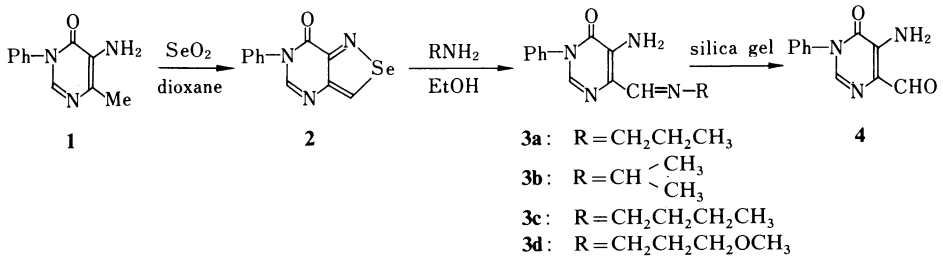

Chart 1

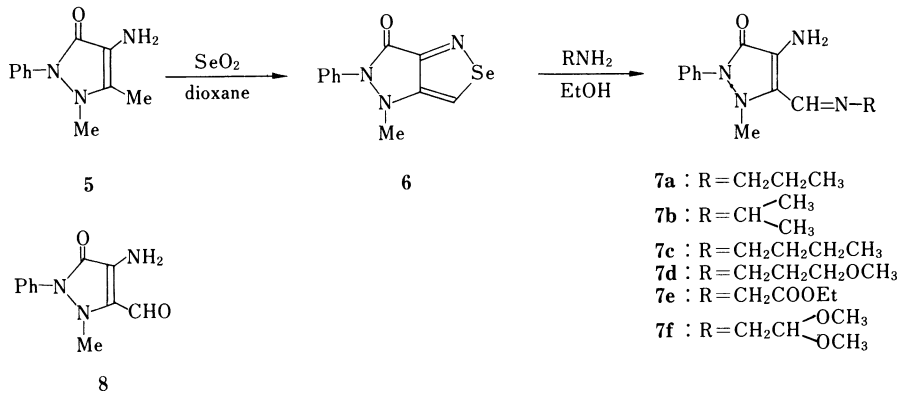

Chart 2

The reaction mechanism in the formation of **3** or **7** from **2** or **6** seems to be as follows. The canonical forms of the fused isoselenazoles can be depicted as in Chart 3. The nucleophilic substitution reaction takes place initially at the carbon atom adjacent to selenium which has exceptionally low electron density. Rupture of the isoselenazole ring followed by deselenation gives **3** or **7**.

Consequently our new method to convert the methyl group of **1** or **5** to an alkyliminomethyl group or formyl group should be convenient and useful for the synthesis of further annelated compounds which might show important pharmacological activities.

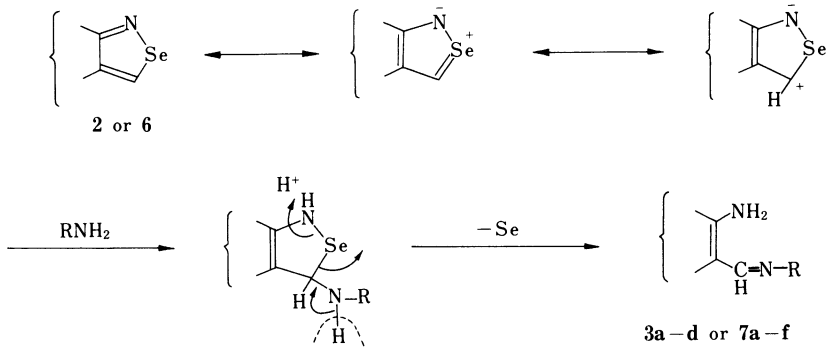

Chart 3

TABLE I. 6-Alkyliminomethyl-5-amino-3-phenyl-4(3*H*)-pyrimidinones

Compd. No.	mp (°C)	Yield (%)	Reaction time (h)	Formula	Analysis (%) Calcd (Found)			MS *m/z* (M^+)
					C	H	N	
3a	151—153	53	7	$C_{14}H_{16}N_4O$	65.61 (65.47)	6.29 (6.06)	21.86 (21.82)	256
3b	138—140	58	24	$C_{14}H_{16}N_4O$	65.61 (65.80)	6.29 (5.98)	21.86 (21.74)	256
3c	135—137	47	7	$C_{15}H_{18}N_4O$	66.65 (66.69)	6.71 (6.41)	20.72 (20.53)	270
3d	124—125	55	7	$C_{15}H_{18}N_4O_2$	62.92 (62.75)	6.34 (6.21)	19.57 (19.81)	286

TABLE II. 3-Alkyliminomethyl-4-amino-2-methyl-1-phenyl-3-pyrazolin-5-ones

Compd. No.	mp (°C)	Yield (%)	Reaction time (h)	Formula	Analysis (%) Calcd (Found)			MS *m/z* (M^+)
					C	H	N	
7a	90—92	92	5	$C_{14}H_{18}N_4O$	65.09 (65.08)	7.02 (6.95)	21.69 (21.67)	258
7b	140—142	95	5	$C_{14}H_{18}N_4O$	65.09 (65.35)	7.02 (7.15)	21.69 (21.54)	258
7c	92—94	97	5	$C_{15}H_{20}N_4O$	66.15 (66.20)	7.40 (7.59)	20.57 (20.76)	272
7d	120—121	90	5	$C_{15}H_{20}N_4O_2$	62.48 (62.32)	6.99 (6.94)	19.43 (19.57)	288
7e	96—97	50	10	$C_{15}H_{18}N_4O_3$	59.59 (59.43)	6.00 (5.81)	18.53 (18.29)	302
7f	82—83	86	5	$C_{15}H_{20}N_4O_3$	59.19 (58.91)	6.62 (6.41)	18.41 (18.55)	304

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were measured with an IR-810 machine from Nihon Bunko Spectroscopic Co., Ltd. Mass spectra (MS) were measured with a Japan Electron Optics Laboratory Co. JMS-DX 300 mass spectrometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Japan Electron Optics Laboratory Co. JNM-MH 100 spectrometer using tetramethylsilane as an internal standard. Abbreviations are as follows: s, singlet; m, multiplet; br, broad.

6-Alkyliminomethyl-3-phenyl-4(3*H*)-pyrimidinones (3a—d)——A mixture of 7-oxo-6-phenyl-6*H*-isoselenazolo[4,3-*d*]pyrimidine[3a] (**2**) (1 mmol) and an alkylamine (10 mmol) in 20 ml ethanol was refluxed for 7 or 24 h. The resulting black substance (Se) was removed by filtration. Solvent and excess alkylamine were distilled off from the filtrate, and the residue was recrystallized from ethanol to give the pure product. Melting points and elemental analytical data are listed in Table I.

5-Amino-6-formyl-3-phenyl-4(3*H*)-pyrimidinone (4)——A solution of 5-amino-3-phenyl-6-propyliminomethyl-4(3*H*)-pyrimidinone (**3a**) 256 mg (1 mmol) in chloroform–methanol (30 : 1) was passed through a silica gel column. The eluate was collected and the solvent was distilled off. The residue was recrystallized from ethanol to give colorless needles of mp 192—194 °C. Yield 196 mg (91%). IR ν_{max}^{KBr} cm^{-1}: 3400, 3290 (NH_2), 1680, 1660 (C=O). MS *m/z*: 215 (M^+). *Anal.* Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.53. Found: C, 61.24; H, 4.20; N, 19.40. ^{1}H-NMR ($CDCl_3$) δ: 9.95 (1H, s, CHO), 7.60 (1H, s, –N–CH=N–), 7.00 (2H, br, NH_2), 7.20—7.55 (5H, m, Ph).

3-Alkyliminomethyl-4-amino-2-methyl-1-phenyl-3-pyrazolin-5-ones (7a—f)——A mixture of 5,6-dihydro-4-

methyl-6-oxo-5-phenyl-4*H*-pyrazolo[4,3-*c*]isoselenazole[6] (**6**) (1 mmol) and an alkylamine (10 mmol) was treated as described for **3a**—**d**. Melting points and elemental analytical data are listed in Table II.

4-Amino-3-formyl-2-methyl-1-phenyl-3-pyrazolin-5-one (8)——A solution of 4-amino-2-methyl-1-phenyl-3-propyliminomethyl-3-pyrazolin-5-one (**7a**) (258 mg, 1 mmol) in chloroform–methanol (30 : 1) was passed through a silica gel column. The eluate was collected and the solvent was distilled off. The residue was extracted with ether. The extract was column chromatographed on silica gel and eluted with ether. The eluate was collected and concentrated. On standing, needles were formed with a red tarry substance. The needles were collected by filtration and washed with a small amount of a mixture of ether–ethanol (1 : 1) to give reddish needles of mp 137—139 °C. Yield 3 mg (1.4%). IR ν_{max}^{KBr} cm^{-1}: 3420, 3250 (NH_2), 1680, 1640 (C=O). MS *m/z*: 217 (M^+).

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