The sodium enolate of formylacetic acid ethyl ester was chosen for conversion of the S^{35}-labeled thiourea after preliminary experiments had shown that it was superior to both ethyl β,β-diethoxypropionate[5] and ethyl β-ethoxyacrylate[5] for this purpose. The requisite sodium enolate of formylacetic acid ethyl ester was prepared by condensation of ethyl formate with ethyl acetate. The procedure was essentially that of Wislicenus[6] except that commercially available sodium methoxide was substituted for metallic sodium as condensing agent. Conditions for the crucial second step of the synthesis of the labeled thiouracil were standardized by a series of condensations of the crude enolate of formylacetic acid ethyl ester with ordinary thiourea before proceeding to conversion of the labeled thiourea. A study of the fate of this labeled thiouracil in the rat indicated a high degree of concentration in the thyroid. Details will be published elsewhere.

EXPERIMENTAL

Sodium enolate of formylacetic acid ethyl ester. To a 1-l. 3-necked round-bottomed flask equipped with a reflux condenser (fitted with a calcium chloride tube), mechanical stirrer, and thermometer, was added 500 ml. of anhydrous ether and 27 g. (0.5 mole) of commercial sodium methoxide. With stirring, a mixture of 49 ml. (44.1 g.; 0.5 mole) of ethyl acetate, and 49 ml. (44.2 g.; 0.6 mole) of ethyl formate was added slowly. The resulting suspension was stirred for 6 hr., allowed to stand for 2 days without stirring and then stirred for 2 days more.

The solid was collected on a Büchner funnel with suction, washed well with anhydrous ether and dried *in vacuo*. The resulting crude product weighed 13.2 g. It was estimated to contain about 42% of the sodium enolate of formylacetic acid ethyl ester, based on the amount of 2-thiouracil isolated on condensation of a sample with an excess of thiourea.

2-Thiouracil-S^{35}. The reaction conditions described below are similar to those of Wheeler and Liddle.[7]

The S^{35}-labeled 2-thiourea was obtained from Tracerlab, Inc., 130 High Street, Boston 10, Mass. The sample used weighed 61 mg. (0.8 millimole) and was stated to contain 8 millicuries of S^{35} activity. It was prepared by Tracerlab to order and was delivered to our laboratory immediately after preparation and determination of activity. The experimental work described below was completed within one week after receipt of the thiourea.

The labeled thiourea was dissolved in 3 ml. of distilled water in a test tube and treated with 660 mg. (a large excess) of crude sodium enolate of formylacetic acid ethyl ester. The test tube was loosely stoppered and heated on the steam bath at 95–100° for 1.5 hr. The reddish solution was cooled to room temperature, filtered to remove a trace of insoluble material and acidified with glacial acetic acid. The precipitate was collected on a small Hirsch funnel with suction, washed with distilled water and ethanol and dried briefly on the steam bath. The product weighed 84 mg. (82% of the theoretical yield based on thiourea), dec. 315° (lit.[7] m.p. *ca.* 340° dec.). A portion was converted to the known[7] S-benzyl derivative by warming with benzyl chloride in dilute aqueous alcoholic sodium hydroxide solution. An 81% yield of product was obtained, m.p. 196–199°. A mixture with an authentic, inactive specimen of 2-benzylthiouracil, m.p. 196–199° (lit.[7] m.p. 192–193°), had m.p. 196–199°. Similar results were obtained when authentic, inactive thiouracil was benzylated. The labeled 2-thiouracil was estimated to contain (0.82 × 8 mc. =) 6.6 mc. of S^{35} activity, and therefore to have a specific activity of (6.6 mc./84 mg. =) 0.079 mc./mg. A direct β-ray count on the substance recorded 2.15 × 10^7 counts/mg./min.

RESEARCH DEPARTMENT
CIBA PHARMACEUTICAL PRODUCTS, INC.
SUMMIT, N. J.

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
NEW YORK, N. Y.

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Potential Purine Antagonists XIV. Synthesis of Some 4-(Substituted amino)pyrazolo-[3,4-*d*]pyrimidines[1]

C. WAYNE NOELL AND ROLAND K. ROBINS

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Recent anti-tumor activity[2] exhibited by certain 4-amino- and 4-alkylaminopyrazolo [3,4-*d*]pyrimidines has prompted the preparation of additional derivatives in this series.

The new 4-(substituted amino)pyrazolo[3,4-*d*]-pyrimidines and 1-methyl-4-(substituted amino)-pyrazolo[3,4-*d*]pyrimidines which have been prepared are listed in Tables I and II. These compounds have been prepared by reaction of the corresponding 4-chloropyrazolo[3,4-*d*]pyrimidine[3,4] with various primary and secondary amines in a manner similar to that previously described.[3,4] When the higher homologs of the alkylamines were employed, it was found convenient to isolate these derivatives as the hydrochloride rather than the free base.

The anti-tumor activity of these compounds will be reported elsewhere at a later date.

EXPERIMENTAL

General method of preparation of 1-methyl-4-(substituted amino)pyrazolo[3,4-d]pyrimidines listed in Table I. Method (A). Ten grams of 1-methyl-4-chloropyrazolo[3,4-*d*]pyrimidine[4] was added to a solution of an equal molar amount of the amine dissolved in 150 ml. of absolute ethanol. The solution was heated on the steam bath for 2 hr., then boiled with charcoal and filtered. Dry hydrogen chloride gas was passed into the cooled filtrate for 20 min. The solution was then allowed to stand overnight and the precipitate filtered

(1) This investigation was supported by research grants C-2105(C2) and C-2105(C3) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

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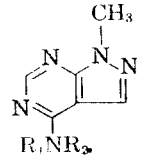
TABLE I

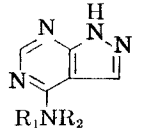
1-METHYL-4-(SUBSTITUTED AMINO)PYRAZOLO[3,4-*d*]PYRIMIDINES



R_1	R_2	M.P., °C.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Meth. of Prepn.	Yield, %	*p*H 1 $\lambda_{max.}$, Mμ	*p*H 1 $\epsilon_{max.}$	*p*H 11 $\lambda_{max.}$, Mμ	*p*H 11 $\epsilon_{max.}$
H	$-CH_2CH(CH_3)_2 \cdot HCl$	210–217	49.4	6.6	29.0	49.5	6.7	28.8	A	63	224.5 267	23,000 14,000	231 285	4,800 15,000
H	$-(CH_2)_2CH(CH_3)_2 \cdot HCl$	214–217	51.6	7.1		51.4	7.2		A	37	224 267	13,300 8,400	233 285	2,500 9,200
H	$-(CH_2)_6CH_3 \cdot HCl$	190–193	55.1	7.8		55.0	7.7		A	30	224 267	15,200 9,400	233 285	3,400 10,400
H	$-(CH_2)_7CH_3 \cdot HCl$	196–199	56.5	8.1		56.3	8.3		A	25	224 267	10,200 6,600	234 285	2,100 7,500
H	$-(CH_2)_2C_6H_5 \cdot HCl$	205–208	57.9	3.8	24.2	58.0	4.2	24.2	A	51	222 267	23,200 13,900	231 285	4,900 14,500
H	$-CH_2CH(CH_2)_3CH_3 \cdot HCl$ C_2H_5	148	56.5	8.1		56.5	7.9		A	32	224 267	20,600 13,200	234 285	3,600 13,400
H	$-CH_2C_6H_4Cl$-*p*	205–206	57.1	4.4	25.5	57.1	4.3	25.6	B	96				
H	$-CH_2CH{=}CH_2 \cdot HCl$	197–203	47.8	4.9	31.0	47.7	5.3	30.7	A	85	224.5 266	20,800 12,000	231.5 284	2,600 13,100
H	$-(CH_2)_{10}CH_3 \cdot HCl$	197–199	60.1	8.9		60.1	9.0		A	42				
H	$-CH_2C_6H_4OCH_3$-*p*	165–166	62.5	5.9	26.0	62.5	5.7	25.8	B	94	226 267	28,800 15,200	228 285	11,000 15,300
CH_3	$-CH(CH_3)_2 \cdot HCl$	186–189	49.8	6.7		49.7	6.4		A	35	226 271	16,900 13,100	234 291	5,300 15,300

TABLE II

4-(SUBSTITUTED AMINO)PYRAZOLO[3,4-*d*]PYRIMIDINES



R_1	R_2	M.P., °C.	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Found C	Found H	Found N	Found Cl	Meth. of Prepn.	Yield, %	*p*H 1 $\lambda_{max.}$ Mμ	*p*H 1 $\epsilon_{max.}$	*p*H 11 $\lambda_{max.}$ Mμ	*p*H 11 $\epsilon_{max.}$
H	—$(CH_2)_4CH_3$·HCl	210–215				14.8				14.5	A	36	265	10,600	279	14,900
H	—$(CH_2)_5CH_3$·HCl	206–208			27.5	13.9			27.1	13.6	A	39	265	12,700	279	17,600
H	—$(CH_2)_6CH_3$·HCl	196–199				13.2				13.0	A	43	264	12,400	278	12,400
H	—$(CH_2)_2CH(CH_3)_2$·HCl	231–235				14.7				14.5	A	37	264	12,000	277	13,900
H	—$(CH_2)_7CH_3$·HCl	213–215				12.6				12.6	A	41	266	26,100	275	19,000
C_2H_5	—$(CH_2)_2CH_3$	165–166	58.7	7.3	34.1		58.3	7.1	34.2		B	47	267		280	
H	—$CH_2CH(CH_3)_2$·HCl	238–242	47.7	6.2		15.7	47.8	6.5		15.4	A	35	266	13,200	271	13,400
H	—$(CH_2)_2N(C_2H_5)_2$·HCl	246–248			31.2	13.2			31.1	13.1	A	80	282	25,700	278	27,000
$(CH_2)_2CH_3$	—$(CH_2)_2CH(C_4H_9)$·HCl	209–213				13.9				14.2	A	30	283	13,000	291	13,500
H	—$CH_2CH(C_2H_5)$·HCl	226–230			24.8	12.6			24.6	12.5	A	41	257	11,000	275	14,400
H	—$(CH_2)_3N(C_2H_5)_2$·HCl	239–240			29.7	12.5			30.1	12.0	A	86	268	11,900	276	13,600
H	—$(CH_2)_2$—C_6H_5·HCl	224–228				12.9				12.9	A	49	267	12,100	270	12,700
H	$CH_2C_6H_4Cl$-*p*	210–211	51.0	3.9			50.7	4.0			C	77	270	12,600	225	11,800
															275	14,000
H	—$(CH_2)_8CH_3$·HCl	222–225				12.0				12.0	A	45	264	11,300	275	11,300
H	—$(CH_2)_{10}CH_3$·HCl	217–220				10.9				10.9	A	41	265	14,400	269	9,200
H	—$(CH_2)_{11}CH_3$·HCl	214–217	60.2	8.8		10.5	60.6	8.8		10.5	A	48	265		272	
H	$CH_2C_6H_4OCH_3$-*p*	209–211	61.3	5.1			61.6	5.3			C	66	270	8,700	227	9,400
															276	10,400
H	$CH_2C_6H_3Cl_2$—2,4	270–271	49.0	3.1			49.4	3.3			C	83	269	11,900	228	8,500
															273	10,900

and washed with ether. The salt thus obtained was recrystallized from boiling absolute ethanol containing a small amount of dry hydrogen chloride. The solution was finally cooled and filtered and the product washed with ether and dried at 110°.

Method (B). Ten grams (0.059 mole) of 1-methyl-4-chloropyrazolo[3,4-*d*]pyrimidine[4] was added to twice the molar amount (0.119 mole) of the amine dissolved in 150 ml. of absolute ethanol. The solution was heated on the steam bath until the volume had been reduced to approximately 50 ml. (6 hr.). The desired 1-methyl-4-(substituted amino)pyrazolo-[3,4-*d*]pyrimidine crystallized upon cooling. The compound was further purified by recrystallization from ethanol.

General method of preparation of 4-(Substituted amino)-pyrazolo[3,4-d]pyrimidines listed in Table II. Method (A). Eight grams of 4-chloropyrazolo[3,4-*d*]pyrimidine[3] (0.053 mole) was added to an equal molar amount of a solution of the amine dissolved in 200 ml. of absolute ethanol. The mixture was heated on the steam bath for 2 hr., boiled with charcoal for 5 min., and filtered. Dry hydrogen chloride was passed into the cooled filtrate for 20 min. and the solution allowed to stand overnight and finally filtered. The crude product was washed with ether and recrystallized from boiling absolute ethanol which contained a small amount of dry hydrogen chloride. The hydrochloride salt was filtered, washed with dry ether, and dried at 110°.

Method (B). Eight grams (0.053 mole) of 4-chloropyrazolo-[3,4-*d*] pyrimidine[3] was added to twice the molar amount (0.106 mole) of the amine, and the ethanolic solution was reduced to 50 ml. by heating on the steam bath. Then 100 ml. of distilled water was added and the solution cooled. The crude product was filtered and purified by recrystallization from a methanol-water solution.

Method (C). This method was the same as Method B except that the ethanolic reaction mixture was heated for 2 hr. on the steam bath and then allowed to cool. The product either crystallized during the reaction period or appeared on cooling the solution overnight. The product was filtered and recrystallized from ethanol.

DEPARTMENT OF CHEMISTRY
NEW MEXICO HIGHLANDS UNIVERSITY
LAS VEGAS, N. M.
DEPARTMENT OF CHEMISTRY
ARIZONA STATE COLLEGE
TEMPE, ARIZ.

The S_N2 Reactivity of β-Fluoroethyl Iodides[1]

JACK HINE AND ROBERT G. GHIRARDELLI

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It has been shown earlier that β-fluorine, chlorine, and bromine substituents all decrease S_N2 reactivity,[2] at least in the reactions of ethyl bromides with sodium thiophenoxide in methanol.[3] We have now studied the effect of one, two, and three β-fluorine substituents on the reactivity of ethyl iodide under the same conditions.

(1) Part VIII in the series "The Effect of Halogen Atoms on the Reactivity of Other Halogen Atoms in the Same Molecule." This work was supported in part by the U. S. Atomic Energy Commission.

(2) For the meaning of the term S_N2, see J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N.Y., 1956, chap. 5.

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EXPERIMENTAL

Reagents. Reagent ethyl iodide (Matheson, n_D^{25} 1.5098) was used as received while the 1,1-difluoro-2-iodoethane and 1,1,1-trifluoro-2-iodoethane purchased were fractionally distilled. Each of the latter compounds had been made by the Columbia Organic Chemicals Co., Columbia, S.C., by the action of sodium iodide on the appropriate *p*-toluenesulfonate.[4] For the difluoroethyl iodide, we found b.p. 86.8–87.1° (740 mm.), $n_D^{25.2}$ 1.4577, d_4^{25} 2.1840, in comparison with previous reports of b.p. 89.5°,[5] $n_D^{12.2}$ 1.46807,[5] $d_4^{12.2}$ 2.24328,[5] d_4^{20} 2.2259.[6] For the trifluoroethyl iodide, b.p. 53.5–54.0° (732 mm.), n_D^{25} 1.3981 (reported,[4] b.p. 55.0°, n_D^{25} 1.3981).

The 2-fluoroethyl iodide used was prepared from 2-fluoroethyl bromide[7] by the action of sodium iodide in acetone. A solution of 30.6 g. (0.24 mole) of 1-bromo-2-fluoroethane and 40 g. (0.29 mole) of sodium iodide in 200 ml. of acetone was refluxed for 4 hr. and then most of the acetone was removed by fractional distillation. When the residue was cool, 60 ml. of water was added, the two resultant layers were separated, and the aqueous layer was extracted with methylene chloride. This extract was combined with the organic layer and fractionated to give 2.6 g., b.p. 94.5–96.5°, 29.6 g., b.p. 96.5–97.0°, and after the addition of a still base (bromobenzene), 6.4 g., b.p. 95.8–96.5° (all at 741 mm.). The total yield was thus 92% and for the middle fraction, n_D^{25} 1.5010, d_4^{25} 2.136, molar refractivity[8] calcd. 24.24, found 24.00. Henne and Renoll report that 1-fluoro-2-iodoethane boils at 98–102° but give no other properties.[10]

The methanol and thiophenol used and the methods of preparing sodium thiophenoxide solutions and titrating for thiophenol have been described previously.[3]

Kinetic runs. The kinetic runs were carried out as described previously[3,11] except that unpainted long-necked Erlenmeyer flasks were used as reaction vessels, 5 ml. of acetic acid was added to stop the reaction and the thiophenol was then titrated in the reaction flask.

Reaction products. Some of the residual solutions from the reaction of trifluoroethyl iodide with sodium thiophenoxide were combined and the methanol removed by heating to 90°. The remaining material was then added to 20 ml. of water and 30 ml. of ether. The ether was evaporated and the residue fractionally distilled in vacuum giving principally a colorless liquid, b.p. 62–63° (5.5 mm.), n_D^{20} 1.4906, d_4^{20} 1.2582, molar refractivity[8] calcd. for $C_6H_5SCH_2CF_3$ 43.47, found 44.21. Analogous treatment of residues from the difluoroethyl iodide reaction gave a product, b.p. 87–89° (7 mm.), n_D^{20} 1.5350, d_4^{20} 1.1977, molar refractivity[8] calcd. for $C_6H_5SCH_2CHF_2$ 43.47, found 45.28.

Calculations. Rate constants were calculated for each point by use of the integrated form of the second order rate equation

$$k = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)}$$

where $a = [RI]_0$, $b = [C_6H_5SNa]_0$, $x = b - [C_6H_5SNa]_t$, t = time (sec.). This equation is derived with the assumption that only one halogen atom (the iodine) is replaced, in

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