oxidate analyzing for 9.4% hydroperoxide. Distillation gave a forerun of 383 g. of 4-vinylcyclohexene, 23 g. of hydroperoxide (68.5%) at 64–66°/0.5 mm., 20.3 g. of pot residue and 3 g. of trap residue. The hydroperoxide was fractionated in a 1-ft. semimicro Vigreux column to give 9 ml. of distillate boiling at a constant 55°/0.5 mm. with $n_D^{25}$ 1.4951 and $D_4^{20}$ 1.0164 and analyzing for 81% hydroperoxide. $M_D$ is 40.9 (calculated $M_D$ 39.2).

*Reduction with sodium sulfite.* To 50 ml. of a stirred 25% solution of sodium sulfite, cooled in an ice bath, was added dropwise 14.1 g. (0.1 mole) of hydroperoxide of 76.8% purity (method C). After 1 hr. the reaction was allowed to reach room temperature and stirred for 1.5 hr. more. The product was extracted with ether and dried over Drierite. After removing the ether, 10 g. of distillate was collected at 46–49°/0.5 mm. It analyzed for 5.25% hydroperoxide (method C). Its infrared spectra were superimposable on that of the starting hydroperoxide, both spectra being obtained with a Baird IR model 4-55 using a 0.03-mm. cell. Both spectra showed a band at 5.8$\mu$ indicating an estimated carbonyl impurity of less than 5%.

*Acid decomposition.* A solution of 14.1 g. (0.1 mole) of hydroperoxide (76.8%—method C) in 80 ml. of glacial acetic acid containing 0.16 ml. of 70% perchloric acid was allowed to stand overnight at room temperature. A slurry of 26 g. of sodium bicarbonate in 150 ml. of water was added dropwise, and the gas evolved passed through a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid. The precipitate formed was identified as acetaldehyde 2,4-dinitrophenylhydrazone by a mixed melting point determination. The decomposition mixture was extracted with ether and the ether washed with sodium bicarbonate and water and dried. Distillation through a Vigreux column gave 5.1 g. of ketone at 64–70°/4 mm., $n_D^{20}$ 1.4818 and a pot residue of 5.0 g. of black tar.

The infrared spectra of the distillate showed the expected bands at 6.0$\mu$ and 6.1$\mu$ as well as a band at 5.8$\mu$ probably due to the unconjugated 3-cyclohexenone. Absorption due to hydroxyl, vinyl unsaturation, or aldehyde carbonyl (C—H stretching) was absent. The ultraviolet spectra showed the reported[3] max. 225 m$\mu$ for 2-cyclohexenone. The semicarbazone melted at 161–162° (reported m.p. 161°, 163°) after one recrystallization from water. The 2,4-dinitrophenylhydrazone after several recrystallizations from alcohol, yielded cerise crystals melting at 180–181° (rapid heating). An authentic sample of 2-cyclohexenone, prepared by oxidizing cyclohexene,[6] yielded an orange derivative melting at the reported[3] 160–161°. Its melting point was not depressed by admixture with the decomposition product derivative. Both 2,4-dinitrophenylhydrazones showed maxima in the ultraviolet at 377 m$\mu$ ($\epsilon$ = 21,000), 285 m$\mu$ and 250 m$\mu$ and a minimum at 310 m$\mu$.

Fractionation of the ketone, from a similar experiment, through a spinning band column gave a fraction at 41°/1 mm. $n_D^{25}$ 1.4950, which had a carbonyl equivalent weight of 99 (calculated for cyclohexenone 96) by hydroxylamine titration.[7]

*Hydrogenation.* Fifteen g. of alcohol, containing 6.34 m. eq. of hydroperoxide impurity, was hydrogenated at 60 lb. pressure using 170 ml. of ethanol as solvent and 0.5 g. of rhodium on alumina as catalyst. The absorption of hydrogen ceased after 0.13 mole was consumed. With 0.2 g. of platinum oxide, a total of 0.256 mole of hydrogen was used. Addition of fresh catalyst did not result in any further reduction. Compensating for the reduction of the hydroperoxide impurity, the hydrogen consumed was 0.242 mole; calculated for vinylcyclohexenol 0.240 mole.

Fractionation of the reduction product gave the following fractions after removal of the solvent: (1) 2.3 g. 100–107.5°/50 mm., $n_D^{25}$ 1.4522; (2) 4.4 g., 107.5–111.5°/50 mm., $n_D^{25}$ 1.4500; (3) 3.8 g., 111.5–119.5°/50 mm., $n_D^{25}$ 1.4600.

*Analysis of hydroperoxide.* Approximately 0.5 g. samples of oxidate were analyzed by refluxing in isopropyl alcohol containing 1 ml. of saturated potassium iodide and titrating the iodine released with sodium thiosulfate (A). The arsenious oxide procedure gave equivalent results.[7] Other iodometric methods were checked using approximately 0.1 g. samples of distilled hydroperoxide. The variations in conditions and the percentage vinylcyclohexene hydroperoxide found for the identical liquid are: (A) 49.1%; (B) 0.5 g. powdered potassium iodide in 100 ml. isopropyl alcohol, 10 ml. acetic acid, 10 ml. acetic anhydride, reflux 30 min., 46.1%; (C) 0.5 g. powdered potassium iodide in 25 ml. acetic acid, 60° for 30 min., 76.8%; (D) as in C, dark for 120 min., 64%; (E) as in C with 1 ml. saturated potassium iodide, 51.9%. Elemental analysis of this sample assuming the remaining component to be vinylcyclohexenol gives agreement with method C. Calcd. for 76.82% $C_8H_{12}O_2$ and 23.18% $C_8H_{12}O$: C, 70.20; H, 8.93. Found: C, 70.09; H, 8.87.

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(6) C. Paquot, *Bull. Soc. Chim.*, **8**, 696 (1941).

(7) S. Siggia, *Quantitative Organic Analysis via Functional Groups* 2nd ed., John Wiley & Sons, New York, 1954.

## Potential Purine Antagonists. XVIII. Preparation of Some 6-Alkylthiopurines and 4-Alkylthiopyrazolo[3,4-*d*]pyrimidines[1]

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Since 6-methylthiopurine has been shown to inhibit R C carcinoma in mice,[2] a number of additional 6-alkylthiopurines have been synthesized in our Laboratory. Since antitumor activity has recently been found with various derivatives of pyrazolo[3,4-*d*]pyrimidine,[3] it seemed of interest to prepare analogous isomeric 4-alkylthiopyrazolo-[3,4-*d*]pyrimidines to see if these derivatives would possess antitumor activity.

Skinner, Shive, *et al.*[4,5] have previously reported the preparation of several 6-alkylthiopurines by alkylation of 6-purinethiol with the appropriate alkyl halide.

Recent preparation of 1-methyl-4-methylthiopyrazolo[3,4-*d*]pyrimidine[6] from 4-chloro-1-methylpyrazolo[3,4-*d*]pyrimidine[6] and methanethiol in a

(1) Supported in part by research grant CY-4008 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) G. S. Tarnowsky and C. C. Stock, *Proc. Am. Assoc. Cancer Res.*, 51 (1955).

(3) H. E. Skipper, R. K. Robins, J. R. Thomson, C. C. Cheng, R. W. Brockman, and F. M. Schabel, Jr., Cancer Research, **17**, 579 (1957).

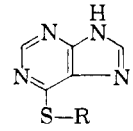
(4) C. G. Skinner, W. Shive, R. G. Ham, D. C. Fitzgerald, Jr., and R. E. Eakin, *J. Am. Chem. Soc.*, **78**, 5097 (1956).

(5) C. G. Skinner, R. G. Ham, D. C. Fitzgerald, Jr., R. E. Eakin, and W. Shive, *J. Org. Chem.*, **21**, 1330 (1956).

(6) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).

TABLE I

6-ALKYLTHIOPURINES



| R | Meth. of Synth. | Recorded M.P. | M.P. | Yield, % | pH 1 $\lambda_{max}$, Mμ | pH 1 ε | pH 11 $\lambda_{max}$, Mμ | pH 11 ε | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_2H_5$ | A | 185[a] | 203–204 | 57 | 225 | 10,800 | 226 | 10,100 | 46.6 | 4.4 | 31.1 | 46.7 | 4.3 | 31.0 |
| | | | | | 298 | 16,200 | 292 | 15,300 | | | | | | |
| *n*-$C_3H_7$ | A | 163–165[a] | 184–185 | 61 | 225 | 9,700 | 224 | 10,400 | 49.4 | 5.2 | 28.8 | 49.6 | 5.6 | 28.9 |
| | | | | | 300 | 15,700 | 294 | 16,500 | | | | | | |
| *iso*-$C_3H_7$ | A | | 243–244 | 43 | 225 | 9,200 | 227 | 10,900 | 49.4 | 5.2 | 28.8 | 49.6 | 5.2 | 29.1 |
| | | | | | 300 | 15,500 | 295 | 14,700 | | | | | | |
| $CH_2CH:CH_2$ | C | | 173–174 | 74 | 221 | 10,200 | 226 | 12,300 | 50.0 | 4.2 | 29.1 | 50.0 | 4.2 | 28.9 |
| | | | | | 296 | 15,900 | 294 | 16,300 | | | | | | |
| *n*-$C_4H_9$ | A | 126–127[a] | 150–151 | 69 | 225 | 9,400 | 228 | 11,400 | 51.9 | 5.7 | 26.9 | 52.2 | 5.7 | 26.9 |
| | | | | | 300 | 15,600 | 294 | 16,200 | | | | | | |
| *sec*-$C_4H_9$ | C | | 197–198 | 61 | 225 | 8,700 | 229 | 9,400 | 51.9 | 5.7 | 26.9 | 52.2 | 5.8 | 27.1 |
| | | | | | 300 | 14,600 | 295 | 13,500 | | | | | | |
| *iso*-$C_4H_9$ | C | | 202–203 | 61 | 226 | 10,000 | 228 | 12,500 | 51.9 | 5.7 | 26.9 | 51.8 | 5.9 | 27.2 |
| | | | | | 300 | 17,300 | 294 | 17,100 | | | | | | |
| *n*-$C_5H_{11}$ | B | 78–79[a] | 107–108 | 58 | 226 | 9,300 | 228 | 11,300 | 54.0 | 6.3 | 25.2 | 54.2 | 6.2 | 24.9 |
| | | | | | 300 | 15,100 | 294 | 16,000 | | | | | | |
| *iso*-$C_5H_{11}$ | C | | 124–125 | 63 | 226 | 9,300 | 228 | 11,300 | 54.0 | 6.3 | 25.2 | 54.2 | 6.0 | 25.4 |
| | | | | | 300 | 15,100 | 294 | 16,000 | | | | | | |
| *n*-$C_6H_{13}$ | B | 77[b] | 95–96 | 43 | 226 | 9,400 | 228 | 12,000 | 55.9 | 6.8 | 23.7 | 55.6 | 7.2 | 23.9 |
| | | | | | 300 | 15,300 | 294 | 16,500 | | | | | | |
| *n*-$C_7H_{15}$ | B | 79–81[b] | 109–110 | 51 | 226 | 9,500 | 228 | 13,000 | 57.6 | 7.2 | 22.4 | 57.6 | 7.0 | 22.2 |
| | | | | | 300 | 16,300 | 294 | 15,500 | | | | | | |
| *n*-$C_8H_{17}$ | B | 78–80[b] | 97–98 | 49 | 226 | 9,600 | 228 | 14,000 | 59.1 | 7.6 | 21.5 | 59.0 | 7.4 | 21.4 |
| | | | | | 300 | 16,300 | 294 | 16,000 | | | | | | |
| *n*-$C_9H_{19}$ | B | | 95–96 | 44 | 226 | 9,700 | 228 | 14,000 | 60.6 | 8.3 | 20.3 | 60.4 | 8.3 | 20.1 |
| | | | | | 300 | 16,300 | 294 | 15,500 | | | | | | |
| *n*-$C_{12}H_{25}$ | B | | 92–93 | 47 | 226 | 9,600 | 228 | 13,000 | 63.9 | 9.4 | 17.5 | 63.7 | 9.4 | 17.4 |
| | | | | | 300 | 16,000 | 294 | 14,000 | | | | | | |

[a] Ref. (4). [b] Ref. (5).

basic solution suggested that 6-alkylthiopurines might be more conveniently prepared from 6-chloropurine. This general reaction proceeded smoothly, and most of the compounds described in Table I were prepared from the corresponding alkanethiols and 6-chloropurine. The melting points for the alkylthiopurines prepared from 6-chloropurine are in general somewhat higher than those recorded for the same compounds previously prepared[7] by alkylation of 6-purinethiol. In this regard 6-ethylthiopurine was prepared by the method of Skinner *et al.*[4] and was found to melt at 203–204° and gave no depression in mixed melting point when mixed with the same compound prepared from 6-chloropurine and ethanethiol.

The 4-alkylthiopyrazolo[3,4-*d*]pyrimidines listed in Table II were prepared similarly from 4-chloropyrazolo[3,4-*d*]pyrimidine[8] and the corresponding alkanethiols. It is interesting to note that the 4-alkylthiopyrazolo(3,4-*d*]pyrimidines melt consistently lower than the alkylthiopurines of similar structure.

## EXPERIMENTAL[9]

*Preparation of the 6-alkylthiopurines listed in Table I. Method (A).* Ten to 15 g. of the appropriate alkylthiol was added to 70 ml. of 4% potassium hydroxide. To this vigorously stirred solution was added 6 g. of 6-chloropurine,[10] and the solution was heated for 30 min. on the steam bath. At the end of this time the *p*H of the solution was adjusted to 7 with dilute hydrochloric acid and the solution chilled. The crude product was filtered and recrystallized twice from ethylacetate.

*Method (B).* To 70 ml. of 4% potassium hydroxide was added 8 g. of the appropriate alkylthiol and 30 ml. of dioxane. This mixture was vigorously stirred and heated at 75° for 30 min. At the end of this period 6 g. of 6-chloropurine[10] was added to the solution and the mixture was stirred and heated at 75° for an additional hour. The *p*H of the solution was adjusted to 7 with dilute hydrochloric acid, and stirring was continued for 30 min. The solution was cooled

(7) Private communication with Dr. C. G. Skinner has revealed that the melting points previously recorded (see refs. 4 and 5) are in error due to their determination on a defective melting point apparatus; see *J. Org. Chem.*, **23**, 2046 (1958).

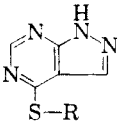
(8) R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

(9) All melting points were taken on the Fisher-Johns melting point apparatus and are uncorrected.

(10) A. Bendich, P. J. Russell, and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954). Purchased from Francis Earle Laboratories, Inc., Peekskill, N. Y.

TABLE II

4-ALKYLTHIOPYRAZOLO[3,4-*d*]PYRIMIDINES



| R | Meth. of Synth. | M.P. | Yield, % | *p*H 1 $\lambda_{max}$, Mμ | *p*H 1 ε | *p*H 11 $\lambda_{max}$, Mμ | *p*H 11 ε | Calcd. N | Found N |
|---|---|---|---|---|---|---|---|---|---|
| $C_2H_5$ | A | 163 | 58 | 300 | 14,400 | 287 | 14,400 | 31.1 | 31.2 |
| *n*-$C_3H_7$ | A | 107 | 55 | 300 | 14,500 | 287 | 15,500 | 28.8 | 28.8 |
| *iso*-$C_3H_7$ | A | 116 | 50 | 300 | 13,900 | 287 | 14,500 | 28.8 | 28.8 |
| *n*-$C_4H_9$ | A | 97–98 | 61 | 300 | 13,500 | 288 | 14,500 | 26.9 | 26.8 |
| *n*-$C_5H_{11}$ | B | 86–87 | 54 | 301 | 12,400 | 289 | 10,400 | 25.2 | 24.9 |
| *n*-$C_6H_{13}$ | B | 82 | 47 | 300 | 16,000 | 289 | 13,200 | 23.7 | 23.4 |
| *n*-$C_7H_{15}$ | B | 68–69 | 49 | 301 | 14,000 | 287 | 14,000 | 22.4 | 22.2 |
| *n*-$C_8H_{17}$ | B | 64 | 45 | 301 | 10,000 | 287 | 14,800 | 21.5 | 21.5 |

overnight and the crude product filtered, washed with ligroin, and recrystallized from an ethylacetate-heptane mixture.

*Method (C).* To 6 g. of 6-purinethiol,[11] dissolved in 100 ml. of 5% potassium hydroxide, was added 7 g. of the appropriate alkyl iodide. The mixture was refluxed and stirred until only one phase was present. The *p*H of the solution was adjusted to 7 with dilute hydrochloric acid and the solution cooled. The crude product was filtered, washed with ligroin, and thoroughly dried. The dried product was placed in the thimble of a soxhlet extractor and extracted continuously with benzene from 4 to 10 hr. The benzene extract was cooled and filtered and the product recrystallized from an ethylacetate-heptane mixture.

*Preparation of the 4-alkylthiopyrazolo[3,4-d]pyrimidines listed in table II. Method (A).* This method is essentially that of method (*A*) used for the preparation of the 6-alkylthiopurines. The only change in procedure was that 4-chloropyrazolo [3,4-*d*]pyrimidine[8] was employed instead of 6-chloropurine. The crude product was recrystallized from an ethylacetate-heptane mixture.

*Method (B).* This method is similar to that of method (*B*) above using 4-chloropyrazolo[3,4-*d*]pyrimidine[8] instead of 6-chloropurine. 4-Octylthiopyrazolo[3,4-*d*]pyrimidine was recrystallized from *n*-heptane rather than a mixture of ethylacetate and *n*-heptane.

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(11) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

## Use of Acetone Dimethyl Acetal in Preparation of Methyl Esters

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When an ester is prepared by the reaction of an alcohol with an acid, the reaction is usually driven to completion by removing the water as an azeotrope with an inert solvent. In the preparation of methyl esters the use of an inert solvent which forms an azeotrope with water is unattractive because of the low water content of azeotropes which boil below methanol. In the preparation of dimethyl oxalate, Bowden[1] used 0.65 mole of concentrated sulfuric acid per mole of oxalic acid. The large amount of sulfuric acid apparently acted as a catalyst and also as a drying agent for the reaction. Clinton and Laskowski[2] reported that "the use of either methylene dichloride or ethylene dichloride as a solvent removes the necessity for continuous drying and gives very high yields of methyl esters." However, in their procedure for each mole of organic acid present there was used three moles of methanol and 300 ml. of solvent.

We have found that by using acetone dimethyl acetal, methyl esters can be prepared conveniently in nearly quantitative yields. The primary function of the acetal appears to be that of a water scavenger and the preparation can be represented by the following two reactions:

$$RCOOH + CH_3OH \xrightarrow{H^+} RCOOCH_3 + H_2O$$

$$H_2O + (CH_3)_2C(OCH_3)_2 \longrightarrow 2CH_3OH + CH_3\overset{O}{\overset{\|}{C}}CH_3$$

For each mole of water formed during the esterification reaction, two moles of methanol are introduced into the reaction solution by the hydrolysis of the acetone dimethyl acetal. As a result the process is self-accelerating. When methanol is present in the initial reaction mixture in excess of 20 mole % of the carboxylic acid groups present, the reaction rate is high throughout the preparation. In the absence of methanol, acetone dimethyl acetal reacts very slowly, if at all, with a carboxylic acid at temperatures up to 75°. (The acetone dimethyl acetal will crack to isopropenyl methyl ether and methanol in the presence of a

(1) E. Bowden in *Org. Syntheses*, **Coll. Vol. II**, 414 (1943).
(2) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, **70**, 3135 (1948).