structure V for the crystalline material. The noncrystalline material was tentatively assigned VI on the basis of its uv and nmr spectra but its elemental analysis was poor. *Anal.* Calcd for $C_{35}H_{45}O_{10}N$: C, 65.71; H, 7.09; N, 2.19. Found: C, 64.31; H, 7.33; N, 1.88.

In a similar manner X was treated with CH_2N_2 and the crude product was treated with NaH–MeI. Again two major products were formed and these were separated and purified by alumina chromatography to give an 11% yield of a crystalline material and a 39% yield of a noncrystalline material. The two crystalline compounds obtained from II and X were identical in every respect including elemental analyses (*Anal.* Calcd for $C_{35}H_{45}O_{10}N$: C, 65.71; H, 7.09; N, 2.19. Found: C, 66.04; H, 7.16; N, 2.44), mixture melting point, and ir and nmr spectra; the two noncrystalline compounds were identical by ir spectra.

Since both X and II are converted to identical derivatives the stereochemistry of the sugar moieties of the two compounds must be identical and X must be O-demethyldecarbamoylnovobiocin (VII).

Synthesis of 5'-Substituted Derivatives of Inosine[1a]

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Growth inhibitory effects are shown by a variety of adenosine analogs in which either the ribose portion or the purine ring skeleton is modified.[2] The inhibition appears in many instances to be related to the tendency for the adeonosine analog to become converted *in vivo* to a nucleoside 5'-phosphate by adenosine kinase action.[2-4] In addition to adenosine derivatives two inosine derivatives, 7-deaza-[5] and 8-aza-9-deazainosines[6] (the 6-hydroxypurine analogs of tubercidin and formycin, respectively), are also inhibitory to mammalian and bacterial systems and it has been suggested[2] that these effects may be associated with enzymatic conversion of these analogs to their ribonucleotides. Support for this possibility is provided by recent evidence[7,8] for the existence in mammalian cells of inosine kinase.

The present report describes the synthesis of some 5'-substituted inosine derivatives, including 5'-amino- and 5'-mercapto-5'-deoxyinosines (4 and 8, respectively) which are potentially capable of becoming phosphorylated at the 5' substituent by an inosine kinase and which might, therefore, exert growth inhibitory effects.

Treatment of 5'-O-(p-tolylsulfonyl)-2',3'-O-isopropylideneinosine (1) with sodium azide in dimethyl sulfoxide furnished the 5'-azido nucleoside 2 in good yield (Scheme I); a minor product was 2',3'-O-isopropylidene-3,5'-cycloinosine (9). 5'-Azido-5'-deoxyinosine (3) could be readily obtained by acidic cleavage of the isopropylidene group of 2. Catalytic hydrogenation of 3 with Raney nickel resulted in essentially complete conversion to 5'-amino-5'-deoxyinosine (4) which, as expected for an alkylamine, reacted with ninhydrin and migrated as a cation upon paper electrophoresis at neutral pH. The nucleoside 4 was conveniently obtained also by hydrogenation of 2 followed by acidic treatment of the resulting 5'-amino-2',3'-O-isopropylidene-5'-deoxyinosine which was not isolated. This latter nucleoside could not be obtained by direct amination of either 1 or 5.

Conversion of the tosyl derivative 1 to 5'-iodo-5'-deoxy-2',3'-O-isopropylideneinosine (5) with NaI in acetone at 100° was reported by Levine and Tipson[9] but identification of the product was inadequate. Holmes and Robins[10] detected the cyclonucleoside 9 among products formed under the conditions of Levine and Tipson and did not report isolation of the 5'-iodo-substituted nucleoside 5. Treatment of 1 with NaI in refluxing acetone furnished the nucleoside 5 in high yield. Removal of the isopropylidene group of 5 occurred smoothly at pH 2 to give 5'-iodo-5'-deoxyinosine (6). The iodo derivative could be converted to the corresponding 5'-thiocyanato derivative with sodium thiocyanate and to the 5'-mercapto derivative (7) with NaSH. Acidic treatment of 7 furnished 5'-mercapto-5'-deoxyinosine (8) in small yield, and paper chromatography indicated that this was due to extensive concomitant fission of the glycosidic bond. The blocked nucleoside 7 was totally converted to hypoxanthine by acidic conditions which had no effect on the glycosidic bond of 2',3'-O-isopropylideneinosine (10).

Holmes and Robins[10] have shown that the tosyl derivative 1 is converted to 2',3'-O-isopropylidene-3,5'-cycloinosine (9) in refluxing dioxane. In the present studies, this intramolecular reaction tended to accompany bimolecular displacement reactions at C-5' of 1 and 5, as noted above for the conversion of 1 to 2. Attempts to prepare 5'-cyano-5'-deoxy-2',3'-O-isopropylideneinosine by reaction of 1 or 5 with NaCN were unsuccessful, as judged by ir spectroscopy of the reaction products, and in some instances yielded principally the cyclonucleoside 9. That formation of 9 is promoted by basic conditions was confirmed by the finding that 5 is converted to 9 at room temperature by NH_4OH; the ease of cyclonucleoside formation is presumably related to electron availability at N-3 in the monoanion of 5 as illustrated by structure 12.

(1) (a) Presented in part at the 155th National Meeting of the American Chemical Society, Division of Medicinal Chemistry, San Francisco, Calif., April 1968. This work was supported by the National Cancer Institute of Canada and the Medical Research Council (Canada) (Grant MA-1591). (b) Author to whom enquiries should be addressed at The Institute for Cancer Research, Philadelphia, Pa. 19111.

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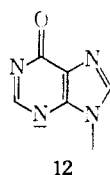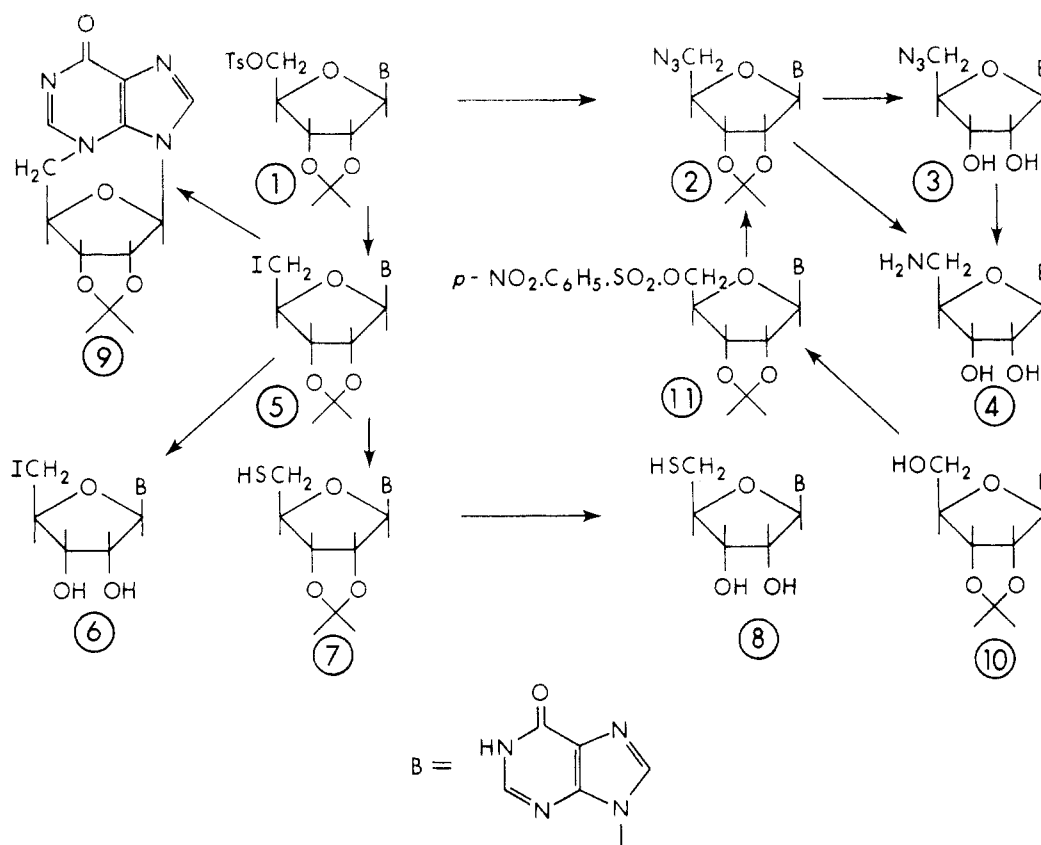
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SCHEME I

B =

12

2′,3′-O-Isopropylideneinosine (10) was converted to the corresponding 5′-O-(p-nitrobenzenesulfonyl) derivative (11). When treated with NaN₃ in DMSO at room temperature nucleoside 11 underwent complete reaction within 5 min and the 5′-azido derivative 2 was isolated in high yield. Under the same conditions the p-toluenesulfonyl derivative 1 did not react. In the present and related series of nucleosides the p-nitrobenzenesulfonyl group may be of wider usefulness than the p-toluenesulfonyl group inasmuch as it enhances reactivity at C-5′ without favoring 3,5′-cyclonucleoside formation over bimolecular displacement.

At a concentration of 1 mM the 5′-deoxyinosine derivatives 4, 6, and 8 inhibited multiplication of L5178Y mouse lymphoma cells by 50% after 48 hr and the 5′-deoxyinosine 3 inhibited by 20%. Under these conditions 6-mercaptopurine was tenfold more inhibitory than 4.[11]

Experimental Section

Paper chromatography was carried out on Whatman No. 1 paper. The solvent systems were as follows: A, i-PrOH–H₂O (7:3); B, i-PrOH–NH₄OH–H₂O (7:1:2); C, n-BuOH–AcOH–H₂O (4:1:5). Rf values are given in Table I. Uv spectra were determined with a Cary Model 15 spectrophotometer and

TABLE I
PAPER CHROMATOGRAPHY

| | Rf values Solvent system | | |
Compd	A	B	C
Hypoxanthine	0.50	0.51	0.42
Inosine	0.50	0.51	0.29
10	0.75	0.67	0.73
1	0.89	0.76	0.91
5	0.89	0.76	0.91
7	0.68	0.55	0.78
2	0.84	0.75	0.90
9	0.71	0.69	0.75
6	0.69	0.55	0.60
8	0.27	0.23	0.30
3	0.67	0.54	0.50
4	...	0.31	0.20

ir spectra were determined in KBr disks in a Perkin-Elmer 137B spectrophotometer. Microanalyses were performed by Dr. A. Bernhardt, Mulheim, Germany, on samples dried in vacuo at 80° for 8 hr over P₂O₅. The values were within ±0.4% of theoretical. Reagent grade pyridine was stored over CaH₂ and used directly. Me₂CO and MeCOEt were distilled after drying (K₂CO₃). Melting points (corrected) were determined on a Kofler micro hot stage.

5′-O-Tosyl-2′,3′-O-isopropylideneinosine (1) was prepared by the method of Levine and Tipson.[9] It crystallized from MeOH–H₂O as white flakes, mp 195–196° (lit.[9] 185–186°). In 0.01 M HCl it showed λmax 249 mμ (ε 10,910) and 229 mμ (ε 15,312); in 0.01 M NaOH, λmax 253 mμ (ε 11,410) and 228 mμ (ε 15,150). It exhibited covalent sulfonate absorption at 8.5 μ[12] and no absorption at 2.8 (free OH) or at 9.8 μ (SO₃⁻). Anal. (C₂₀H₂₂N₄O₇S) C, H, N, S.

5′-Iodo-5′-deoxy-2′,3′-O-isopropylideneinosine (5).—To a solution of 1 (8.0 g, dried at 80° (0.1 mm) over P₂O₅ for 10 hr) in dry Me₂CO (400 ml), was added NaI (20.0 g) and the mixture

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was refluxed for 8 hr under anhydrous conditions. With shorter reaction times conversion was incomplete as shown by the persistence of absorption at 220 mμ in the product due to the tosyl function. Sodium tosylate (3.1 g, theoretical 3.11 g) was removed by filtration. Na₂SO₃ (5 ml of 10% aqueous solution) was added to the acetone solution and solvent was removed under reduced pressure at 30°, leaving a paste which was shaken with a mixture of H₂O (150 ml) and EtOAc (400 ml). The H₂O was saturated with NaCl and again extracted (EtOAc). The ethyl acetate was concentrated to ca. 60 ml and chilled overnight to yield fine needles of product (5.20 g), mp 194–195°. The material was homogeneous on paper chromatograms (solvents A, B, and C) and was used directly for subsequent experiments. The mother liquors gave an additional 0.4 g, mp 185–187° dec; total yield 77%. Crystallization from MeOH–H₂O gave white needles, mp 197–198° dec. *Anal.* ($C_{13}H_{15}IN_4O_4 \cdot CH_3OH \cdot 0.5$-$H_2O$) C, H, N, I.

Crystallization from Me₂CO gave anhydrous material as fine needles: mp 203–204° dec; in 0.01 *M* HCl, λ_{max} 248 mμ (ε 12,150) and λ_{min} 222 mμ (ε 2750); in 0.01 *M* NaOH, λ_{max} 253 mμ (ε 13,100) and λ_{min} 223 mμ (ε 2066). *Anal.* ($C_{13}H_{15}IN_4O_4$) C, H, N.

5′-Mercapto-5′-deoxy-2′,3′-O-isopropylideneinosine (7).—To a stirred solution of NaSH (6.0 g) in MeOH (500 ml) and H₂O (100 ml) was added **5** (2.0 g) at room temperature. H₂S was bubbled in for 20 min. The flask was stoppered and the mixture stirred at 4° for 72 hr. Volatiles were removed *in vacuo* and the gum was dissolved in ice-cold H₂O (170 ml) containing β-mercaptoethanol (2.0 ml) and acidified with 6 *N* AcOH to pH 4.5. The suspension was concentrated to half-volume under reduced pressure and the precipitate was collected by centrifugation and washed with cold aqueous 0.05 *M* β-mercaptoethanol. The product was dissolved in 0.05 *M* NH₄OH (175 ml) containing mercaptoethanol (0.05 *M*), the solution was freed of insolubles, and the pH was adjusted to 4.5 to give product (980 mg), mp 199–200° dec as a white amorphous solid. This material was homogeneous on paper chromatograms in solvents A, B, and C. Vacuum concentration of the mother liquors to 40 ml gave further product (350 mg) which contained ca. 5% of **5**. A suspension of this product in 0.05 *M* β-mercaptoethanol (30 ml) was adjusted to pH 7.0 with NH₄OH and extracted (EtOAc, two 15-ml portions). The pH of the aqueous phase was adjusted to 4.5 to give a second crop (220 mg) of product, mp 204–205° dec, which was chromatographically homogeneous. The combined product (1.2 g) was dissolved in 1.2 l. of boiling 0.05 *M* aqueous β-mercaptoethanol and the solution was concentrated under reduced pressure to ca. 80 ml. The white microcrystals were washed (EtOH and Me₂CO) to give 0.96 g of the monohydrate: mp 232–233° dec; in 0.01 *M* HCl, λ_{max} 248 mμ (ε 11,600) and λ_{min} 220 mμ (2980); in 0.01 *M* NaOH, λ_{max} 253 mμ (ε12,220) and λ_{min} 226 mμ (ε 3976). *Anal.* ($C_{13}H_{16}N_4O_4S \cdot H_2O$) C, H, N, S.

5′-Mercapto-5′-deoxyinosine (8).—A suspension of **7** (200 mg) in aqueous 2.5% AcOH (100 ml) containing 1 ml of β-mercaptoethanol was heated under reflux for 30 min. The resulting solution was immediately cooled to 5°. Chromatography in *i*-PrOH–NH₄OH–H₂O (70:5:25) showed two major uv-absorbing spots with R_f values 0.47 and 0.20 which corresponded to starting material and product, respectively; a minor spot of R_f 0.38 corresponded to hypoxanthine. The solvent was removed from the reaction mixture at 0.1 mm (finally at 20°). The residual gum was dissolved in 10 ml of a mixture of *i*-PrOH–NH₄OH–H₂O–HSCH₂CH₂OH (700:100:190:10), centrifuged from traces of insoluble material, and applied to a 2.5 × 75 cm column of cellulose powder (Whatman standard grade). The column was developed with the same solvent mixture and fractions (11–12 ml) were collected. Chromatography (solvent B) showed that fractions 36–50 contained most of the desired material (R_f 0.2) and also contained a small amount of a component (R_f 0.5) which was presumably starting material. Fractions with this composition from four such columns were combined and evaporated to dryness *in vacuo*. The residual gum was triturated several times with EtOH and solvent was removed *in vacuo* to give the crude mercapto compound as a semisolid. This was dissolved in ca. 0.1 ml of water, β-mercaptoethanol was added, and after successive additions and evaporations of EtOH a white amorphous powder was obtained; this was collected and washed (Me₂CO, two 3-ml portions) to yield crude material (150 mg), mp 194–196° dec. This material was about 95% pure as judged by paper chromatography in solvent B. Crystallization from H₂O (ca. 0.5 ml) and EtOH (ca. 10 ml) in the presence

of β-mercaptoethanol gave a microcrystalline solid (70 mg): mp 216–217° dec; in 0.01 *M* HCl, λ_{max} 248 mμ (ε 11,740), λ_{min} 219 mμ (ε 2884); in 0.1 *N* NaOH, λ_{max} 253 mμ (ε 12,770), λ_{min} 225 mμ (ε 3709). *Anal.* ($C_{10}H_{12}N_4O_4S \cdot 2H_2O$) C, N, S; H: calcd, 5.00; found, 4.34.

When the reaction time was increased to 1 hr the major product was hypoxanthine. Under similar conditions 2′,3′-O-isopropylideneinosine (**10**) even after 2 hr of reaction gave inosine as the only uv-absorbing material in addition to 5–10% of starting material.

5′-Thiocyanato-5′-deoxy-2′,3′-O-isopropylideneinosine.—To a solution of sodium thiocyanate (820 mg) in 50 ml of MeCOEt was added **5** (420 mg), and the mixture was refluxed for 8 hr. Solvent was removed at 30° under reduced pressure, and the brown residue was dissolved in H₂O (40 ml) and extracted into EtOAc (three 100-ml portions). The EtOAc was washed with Na₂SO₃ (two 10-ml portions) then H₂O and evaporated to dryness. The residual solid (210.0 mg) yielded 80 mg of a microcrystalline solid, mp 185–186°, from MeOH–H₂O. Two crystallizations from EtOH then gave the product (60 mg) as colorless needles: mp 189–190°; in 0.01 *M* HCl, λ_{max} 249 mμ (ε 12,280) and λ_{min} 220 mμ (ε 3072); in 0.01 *M* NaOH, λ_{max} 251 mμ (ε 13,520) and λ_{min} 220 mμ (ε 9768). Ir absorption due to the thiocyanate group was present at 4.65 μ. *Anal.* ($C_{14}H_{15}N_5O_4S$) C, H, N, S.

5′-Iodo-5′-deoxyinosine (6).—A suspension of 5.8 g of **5** in 500 ml of HCl, pH 2, was stirred in a bath at 70–80° for 1.75 hr. The resulting solution was concentrated under reduced pressure to ca. 80 ml and the crystalline precipitate was collected and washed (H₂O, Me₂CO) to yield 4 g of product. The mother liquor was neutralized (NH₄OH) and concentrated to give an additional 0.5 g of product (total yield, 86%). Paper chromatography in systems A, B, and C showed only one spot. For analysis the product was obtained from EtOH–H₂O (9:1) as white needles: mp 190° dec; in 0.01 *N* HCl, λ_{max} 248 mμ (ε 11,960) and λ_{min} 221 mμ (ε 3445); in 0.01 *N* NaOH, λ_{max} 253 mμ (ε 13,371), λ_{min} 228 mμ (ε 5265). *Anal.* ($C_{10}H_{11}IN_4O_4$) C, H, I, N.

5′-Azido-5′-deoxy-2′,3′-O-isopropylideneinosine (2).—A mixture of **1** (7 g, 15.2 mmoles) and NaN₃ (7 g, 108 mmoles) in 35 ml of anhydrous DMSO was stirred for 20 min in a bath at 90–100°. Paper chromatography in *n*-BuOH–AcOH–H₂O (5:2:3) showed that ca. 80% of the starting material had been converted to **2** and ca. 20% to **9**. The reaction mixture was diluted with H₂O (100 ml) and extracted with CHCl₃ (350 ml). Evaporation of CHCl₃ and trituration of the residue with a small volume of H₂O yielded 3.8 g (73%) of crystalline product which showed only one spot on paper chromatography in systems A, B, C. Crystallization from H₂O gave white prisms, mp 222° dec. The product showed strong absorption at 4.75 μ corresponding to the azido function. At pH 4 λ_{max} was 248 mμ and λ_{min} was 223 mμ; at pH 11, λ_{max} was 253 mμ and λ_{min} was 225 mμ. *Anal.* ($C_{13}H_{15}N_7O_4 \cdot 0.5H_2O$) C, H, N.

5′-Azido-5′-deoxyinosine (3).—A mixture of **2** (3.6 g) and 400 ml of HCl, pH 2, was heated under stirring in a bath at 70–80° for 1.5 hr. The solution was evaporated to dryness *in vacuo* (finally at 0.1 mm), the residue was dissolved (H₂O), and traces of HCl were neutralized with NH₄OH. Removal of H₂O gave a gum which formed a white solid (2 g, 65% yield) after several additions and evaporations of CHCl₃. This material showed a single spot on paper chromatography in systems A, B, and C and was used directly for the preparation of 5′-amino-5′-deoxyinosine (**4**). Attempts to crystallize the product failed. It separated as a gelatinous precipitate upon cooling its solution in hot ethanol. After two such purifications it had mp 161° dec (prior softening). At pH 4, λ_{max} was 248 mμ, λ_{min} 223 mμ; at pH 11, λ_{max} was 253 mμ, λ_{min} 225 mμ. *Anal.* ($C_{10}H_{11}N_7O_4$) C, H, N.

5′-Amino-5′-deoxyinosine (4). (a) From 3.—Compound **3** (3 g) was dissolved in 100 ml of boiling H₂O. Heating was discontinued and Raney nickel W2 (from ca. 4 g of Ni–Al alloy) was added. When N₂ evolution ceased hydrogenation was carried out at a pressure of ca. 2.8 kg/cm². The mixture was warmed to dissolve precipitated amine and was filtered from catalyst. Cooling gave 2.2 g (75.5%) of white needles which were washed (H₂O, EtOH). Paper chromatography of this product in systems B and C showed a single uv-absorbing spot which gave a positive ninhydrin spray test. After recrystallization from H₂O it had mp 179° dec; at pH 4, λ_{max} 248 mμ (ε 12,200), λ_{min} 219 mμ (ε 1150); at pH 11, λ_{max} 253 mμ (ε 13,200), λ_{min} 224 mμ (ε 2800). *Anal.* ($C_{10}H_{13}N_5O_4 \cdot H_2O$) C, H, N.

(b) From 2.—Compound **2** (1 g) was dissolved in 20 ml of

H₂O, and Raney nickel W2 (from ca. 1.5 g of Ni–Al alloy) was added following which hydrogenation was carried out as in method a. After removal of catalyst 1 equiv of HCl was added and the solution was extracted (CHCl₃) to remove traces of starting material. The aqueous layer was evaporated *in vacuo* to small volume and the amine hydrochloride precipitated with acetone. To remove the isopropylidene group a solution of 0.5 g of this product in 25 ml of HCl (pH 2) was heated for 1 hr at 70–80°. After removal of most of the H₂O the hydrochloride was precipitated with acetone. Reprecipitation yielded 300 mg (69% from the above hydrochloride), mp 217°. *Anal.* (C₁₀H₁₃-N₅O₄·HCl·H₂O) C, H, N.

2′,3′-O-Isopropylidene-3,5′-cycloinosine (9).—A suspension of 5 (1 g) in 5 ml of concentrated NH₄OH was stirred for 24 hr. The crystalline product (0.59 g, 80.5%) was filtered and washed (H₂O); upon chromatography in systems A, B, and C it showed only one spot. Recrystallization (EtOH) gave white plates: mp 266° dec; at pH 4, λ_max 253 mμ (ε 8430); at pH 11, λ_max 256 mμ (ε 8430). *Anal.* (C₁₃H₁₄N₄O₄·H₂O) C, H, N. Holmes and Robins[10] also obtained a monohydrate.

5′-O-(p-Nitrobenzenesulfonyl)-2′,3′-O-isopropylideneinosine (11).—p-Nitrobenzenesulfonyl chloride (850 mg) was added to a suspension of dry 2′,3′-O-isopropylideneinosine (10) (800 mg) in 6 ml of anhydrous pyridine cooled in ice. The mixture was shaken until the 2′,3′-O-isopropylideneinosine dissolved (15 min) and set aside for 10 hr at 2°. Pyridine was removed *in vacuo* and the residual gum was dissolved at 2° with 80 ml of CHCl₃ and the solution was extracted at 2° with 0.01 N HCl (two 30-ml portions). The CHCl₃ solution was dried (Na₂SO₄) and concentrated *in vacuo* to ca. 20 ml. C₆H₆ (15 ml) and Me₂CO (15 ml) were added and the volume was reduced *in vacuo* to 10–15 ml to give 0.77 g (60%) of white crystals, mp 181° dec. The product gave only one uv-absorbing spot on paper chromatography (solvents A and C) and tlc on silica gel in CHCl₃–CH₃OH (93:7) (R_f 0.45). In H₂O (pH 4) or CH₃OH, λ_max was 248 mμ. At pH 4, ε was 15,900; this high value is presumably due to contribution from the p-nitrobenzenesulfonoxy group, since methyl p-nitrobenzenesulfonate in EtOH has λ_max 250 mμ (ε 11,200).[13] Crystallization (Me₂CO) gave needles, mp 181°. *Anal.* (C₁₉H₁₉N₅O₈S) C, H, N.

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Acylations of Some 2-Amino-6-halo-
and 2-Amino-6-alkylthiopurines[1]

ELIZABETH DYER AND CARL E. MINNIER

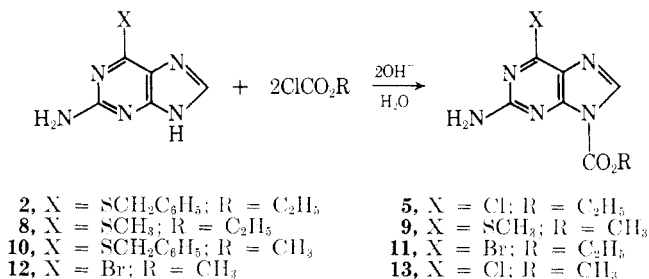*University of Delaware, Newark, Delaware 19711*

The present work is a continuation of a study of acylation of purines[2,3] which involves the preparation of derivatives of possible value in cancer chemotherapy. Included in the current work are carboxylate derivatives of 2-aminopurine-6-thione and of 2-amino-6-chloropurine, both of which in the free state have tumor-inhibitory properties.[4,5]

The 2-amino group in purines is known to react with both aliphatic and aromatic anhydrides[6–9] to yield the

(1) (a) This investigation was supported by the Public Health Service Research Grant No. CA-03477 from the National Cancer Institute. (b) Abstracts from the Ph.D. thesis of C. E. M. (1968), University of Delaware.

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corresponding acylamido derivatives and, when the work-up does not prevent isolation, the purine ring is also acylated.[6,7,9] This is similar to the reactivity of the 6-amino group of adenine.[10–12] However, the 6-amino group of adenine is unreactive toward ethyl chloroformate in aqueous base; acylation occurs on the purine nucleus.[3]

The current results show that the 2-amino group also is unreactive toward alkyl chloroformates under Schotten–Baumann conditions. A number of 2-amino-6-halo- and 2-amino-6-alkylthiopurines yielded mono-acyl derivatives (Table I) when treated with excess ethyl or methyl chloroformate and the site of acylation was shown to be the imidazole ring.

2, X = SCH₂C₆H₅; R = C₂H₅
8, X = SCH₃; R = C₂H₅
10, X = SCH₂C₆H₅; R = CH₃
12, X = Br; R = CH₃

5, X = Cl; R = C₂H₅
9, X = SCH₃; R = CH₃
11, X = Br; R = C₂H₅
13, X = Cl; R = CH₃

The 2-amino group was excluded as the site of acylation by an independent synthesis based on the known 2-acetamido-6-benzylthiopurine[6] (3), since the reaction of ethyl chloroformate with 3 gave the same compound 4 as did the reaction of Ac₂O with ethyl 2-amino-6-benzylthiopurine-9-carboxylate (2) (Scheme I).

SCHEME I
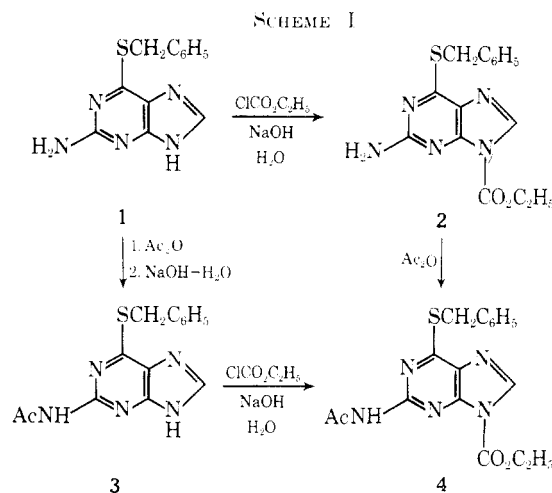
The preparation of carbethoxy derivatives of 2-aminopurine-6-thione and 2-amino-6-selenopurine was accomplished by the action of thiourea and selenourea on 5. Although these reagents have been widely used with 6-chloropurine and its derivatives,[13–16] little use of this reagent has been made with 2-amino-6-chloropurine.[17]

In the current work the reaction of thiourea with 5 in refluxing EtOH gave 2-(2-amino-9-carbethoxypurin-

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