Anal. Calcd. for $C_7H_5ClN_2O_2$: C, 45.54; H, 2.73. Found: C, 45.33; H, 2.78.

4-Chloro-5-methoxybenzofurazan (XX).—A solution of 13.6 g. (0.1 mole) of benzofurazan oxide, prepared by a method previously described,[29] in 44.5 ml. of concentrated sulfuric acid was stirred magnetically and maintained at 5–12° during the addition over a period of 45 min. of a mixture of 5 ml. of fuming nitric acid (min. 90%) and 20 ml. of concentrated sulfuric acid. The stirred reaction mixture was cooled in an ice bath for an additional 1.5 hr. and then poured into ice–water. The solid was collected by suction filtration, washed with water, and recrystallized from 100 ml. of glacial acetic acid (Norit) to give 9.8 g. (54%) of **4(7)-nitrobenzofurazan oxide (XVI)**, m.p. 141.6–143.2° (lit.[28] m.p. 143°).

Reduction of 0.91 g. (0.005 mole) of XVI with triphenylphosphine in refluxing xylene according to the procedure[10] described for the preparation of 5-nitrobenzofurazan (XVII) gave on sublimation 0.37 g. (45%) of **4-nitrobenzofurazan (XIX)**, m.p. 96.6–98.2° (lit.[30] m.p. 98°).

The procedure for the conversion of XIX to 4-chloro-5-methoxybenzofurazan (XX) was identical to that described for the conversion of XVII to 5-chloro-4-methoxybenzofurazan (XVIII). From 0.20 g. (0.0012 mole) of XIX was obtained on sublimation 0.15 g. (67%) of 4-chloro-5-methoxybenzofurazan (XX) with m.p. 130.2–130.8°. Three recrystallizations of the sublimate from 95% ethanol sharpened the m.p. to 130.4–130.8°. Mixture melting point determination and comparison of infrared spectra showed this material to be identical with sample of XX obtained by deoxygenation of 4-chloro-5-methoxybenzofurazan oxide (III) as subsequently described.

Treatment of 0.70 g. (0.0035 mole) of III with 1.0 g. (0.0038 mole) of triphenylphosphine in 35 ml. of refluxing xylene according to the method[10] described for the preparation of 5-nitrobenzofurazan (XVII) gave 0.53 g. (82%) of 4-chloro-5-methoxybenzofurazan (XX) which melted at 129.0–130.2° after one recrystallization from 95% ethanol. Two subsequent recrystallizations from 95% ethanol gave pale yellow crystals of XX melting at 130.2–130.6°.

Anal. Calcd. for $C_7H_5ClN_2O_2$: C, 45.54; H, 2.73. Found: C, 45.60; H, 2.80.

Mechanistic Evidence.—A mechanically stirred solution of 3.4 g. (0.02 mole) of 4-methoxy-2-nitroaniline and 3.4 g. (0.05 mole) of potassium hydroxide in 200 ml. of methanol was heated to 50° and 400 ml. of an aqueous solution of sodium hypochlorite[15] was added. The reaction mixture was cooled and filtered by suction to give 2.4 g. (72%) of **5(6)-methoxybenzofurazan oxide**, m.p. 112–115° (lit.[28] m.p. 118°). The infrared spectrum of this material showed the absence of several intense peaks characteristic of 4-chloro-5-methoxybenzofurazan oxide (III).

A mechanically stirred solution of 3.4 g. (0.02 mole) of 4-chloro-2-nitroaniline and 5.3 g. (0.08 mole) of potassium hydroxide in 200 ml. of methanol was heated to 50° and 400 ml. of an aqueous solution of sodium hypochlorite[15] was added. The reaction mixture was cooled and the precipitate was collected and recrystallized from methanol to give 2.1 g. (63%) of **5(6)-chlorobenzofurazan oxide**, m.p. 43–45° (lit.[28] m.p. 48°). The infrared spectrum of this material was essentially identical with that of an authentic sample of 5(6)-chlorobenzofurazan oxide and showed the absence of several intense peaks characteristic of 5-chloro-4-methoxybenzofurazan oxide (II).

(29) F. B. Mallory, *Org. Syn.*, **37**, 1 (1957).
(30) P. Drost, *Ann.*, **307**, 49 (1899).

Electron Density and Orientation of Nucleophilic Substitution in the Purine Ring[1]

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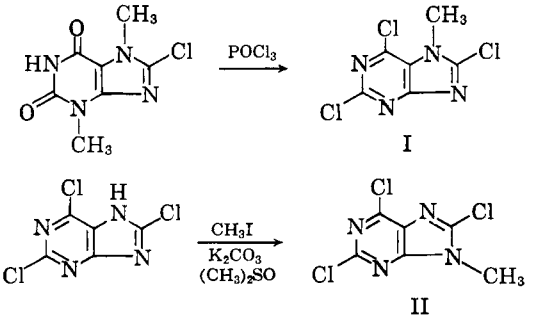
The poor correlation between various electron density calculations and experimental observations relative to the purine ring has resulted in a careful re-examination of nucleophilic substitution in that ring system. It now has been observed that the position of nucleophilic attack can be changed by temporarily blocking the imidazole hydrogen which prevents anion formation in the presence of strong nucleophiles. Acid-catalyzed nucleophilic displacement also may result in a change of orientation. These effects are discussed in terms of a unified theory. It is suggested that similar results might be expected from other related nitrogen heterocyclic systems.

Nucleophilic attack by various reagents on 2,6,8-trichloropurine was first studied by Fischer[2] and extended by later investigators.[3–8] In all cases, with strong bases, nucleophilic displacement occurs first at position 6 followed by position 2 and finally position 8. The reactivities of the various chlorine atoms are such that selective substitution often can be accomplished under the appropriate reaction conditions. When 7-methyl-2,6,8-trichloropurine (I) or 9-methyl-2,6,8-trichloropurine (II) was similarly studied by Fischer,[9] he found that in most instances substitution occurred first at position 8. This would seem at first inspection to be at variance with expectation since modern theory would require that the methyl group at position 7 or 9 should, by the inductive effect, increase the electron density in the imidazole ring and thus favor attack by a nucleophilic reagent in the pyrimidine ring (position 6). Recent electron density calculations for purine[10] would predict nucleophilic substitution at position 6 followed by 2 then 8. Pullman[11] has calculated the localization energy for nucleophilic attack on the purine nucleus and has taken into account induced polarization under these conditions. According to these calculations there is an equal possibility for nucleophilic attack at either position 6 or 8 of the purine ring. Electron density calculations by Mason[12] for nucleophilic attack predict position

(1) This research was supported by grant NSF-G13291 from the National Science Foundation.
(2) E. Fischer, *Ber.*, **30**, 2220, 2226 (1897).
(3) R. K. Robins and B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 3624 (1952).
(4) J. Baddiley, J. G. Buchanan, F. J. Hawker, and J. E. Stephenson, *J. Chem. Soc.*, 4659 (1956).
(5) S. R. Breshears, S. S. Wang, S. G. Bechtolt, and B. E. Christensen, *J. Am. Chem. Soc.*, **81**, 3789 (1959).
(6) R. K. Robins, *J. Org. Chem.*, **26**, 447 (1961).
(7) H. Ballweg, *Ann.*, **649**, 114 (1961).
(8) B. G. Boldyrev and R. G. Makitra, *J. Appl. Chem. USSR*, **28**, 399 (1955).
(9) (a) E. Fischer, *Ber.*, **28**, 2490 (1895); (b) **30**, 1846 (1897); (c) **31**, 104 (1898); (d) **32**, 267 (1899).
(10) R. L. Miller and P. G. Lykos, *Tetrahedron Letters*, 493 (1962); R. L. Miller, P. G. Lykos, and H. N. Schmeising, *J. Am. Chem. Soc.*, **84**, 4623 (1962).
(11) B. Pullman, *J. Chem. Soc.*, 1621 (1959).
(12) S. F. Mason, in "The Chemistry and Biology of Purines," a Ciba Foundation Symposium, Wolstenholme and O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p. 72.

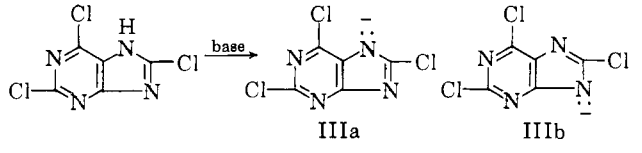
8 most susceptible, followed by position 6 then position 2 of the purine ring.

In an effort to study this problem it was decided to reinvestigate the earlier work of Fischer with 7- and 9-methyl-2,6,8-trichloropurine. Since Fischer prepared these derivatives (I and II) by sealed-tube chlorination procedures,[9] new methods were devised which now make I and II readily available. 7-Methyl-2,6,8-trichloropurine (I) was prepared by the action of phosphoryl chloride on 8-chlorotheobromine. 9-Methyl-2,6,8-trichloropurine (II) was prepared most readily by the methylation of 2,6,8-trichloropurine[6] in dimethyl sulfoxide with methyl iodide patterned after the general method employed by Montgomery and Temple[13] for



alkylation of 6-chloropurine. In every instance studied, nucleophilic attack on I and II did indeed give the products noted by Fischer,[9] and in all cases structural assignments were verified. It should be noted that 6,8-dichloropurine[14] is similar to 2,6,8-trichloropurine in that strong bases attack position 6 in preference to 8.

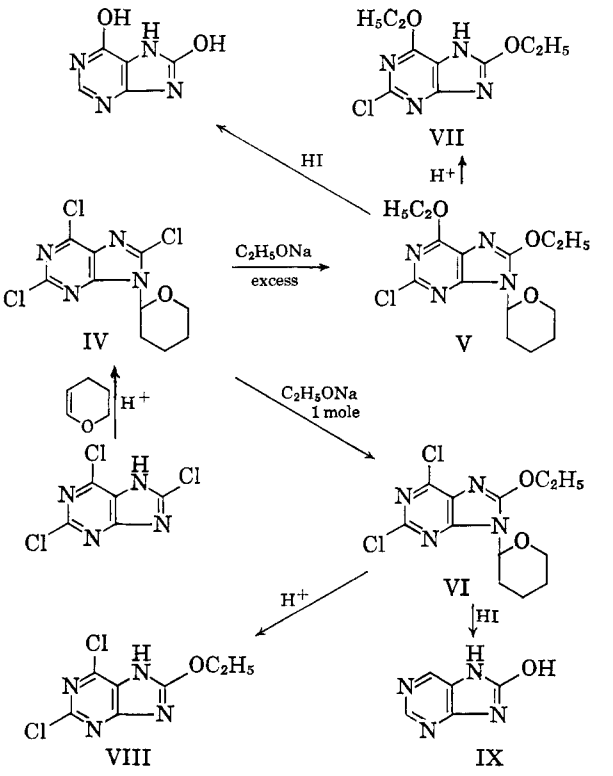
An explanation is now proposed which will account for all known facts regarding nucleophilic displacement in the purine ring and which may be extended to other heterocyclic systems. In the case of the reaction of strong bases, such as hydroxide, alkoxide, alkylamines, alkyl mercaptides, etc., with 2,6,8-trichloropurine, the first step involves the removal of the acidic proton from the imidazole ring. Thus, the species which actually reacts with the excess nucleophile is in reality the anion which is stabilized by resonance. Thus, the anions IIIa and IIIb actually increase the electron density at



position 8 and make nucleophilic attack at this position more difficult. Hence, nucleophilic attack under these conditions occurs preferentially at position 6. In the instances where an imidazole anion cannot form, *i.e.*, 7- and 9-methyl-2,6,8-trichloropurine, nucleophilic substitution occurs preferentially (or equally as well) at position 8. In order to examine this hypothesis more closely, it was proposed to block the imidazole anion formation by some group which could readily be removed. Thus, one should be able to control the orientation of nucleophilic displacement by this means. The blocking group chosen for study was the tetrahydropyranyl

(13) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **83**, 630 (1961).

(14) R. K. Robins, *ibid.*, **80**, 6671 (1958).

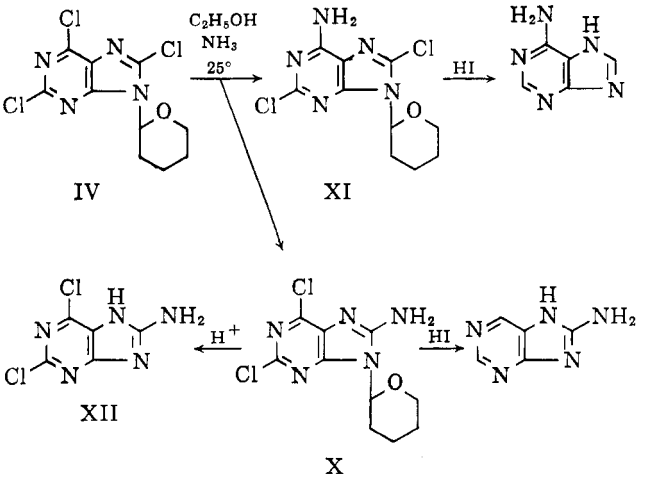


SCHEME 1

group since 9-(tetrahydro-2′-pyranyl)purines[15] are easily prepared, and the tetrahydropyranyl group is readily removed with acid. 2,6,8-Trichloropurine and 2,3-dihydropyran readily gave 9-(tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV) in good yield. The structure of IV was established by comparison of the ultraviolet absorption spectra with those of the model compounds I and II. When IV was treated with excess sodium ethylate in ethanol at room temperature, 2-chloro-6,8-diethoxy - 9 - (tetrahydro - 2′ - pyranyl)purine (V) was obtained in good yield. The structure of V was established by treatment with hydriodic acid which yielded 6,8-dihydroxypurine.[14] When only one mole of sodium ethoxide was employed, the major product was the 8-ethoxy derivative (VI), although a small amount of 6-ethoxy-2,8-dichloro-9-(tetrahydro-2′-pyranyl)purine was detected. The structure of VI was determined by conversion to 8-hydroxypurine with hydriodic acid. Mild acid hydrolysis of VI and V gave an excellent yield of 2,6-dichloro-8-ethoxypurine (VIII) and 2-chloro-6,8-diethoxypurine (VII), respectively. The syntheses of VII and VIII are recorded here for the first time since these compounds are inaccessible by other routes. Thus, in effect, 2,6-dichloro-8-ethoxypurine (VIII) has been prepared from 2,6,8-trichloropurine which by direct reaction with ethoxide ion yields 2,8-dichloro-6-ethoxypurine.[2] Similarly, an excess of sodium ethoxide and 2,6,8-trichloropurine yields 8-chloro-2,6-diethoxypurine.[2] With IV and excess sodium ethoxide in ethanol, 2-chloro-6,8-diethoxypurine (VII) was obtained *via* V.

An extension of this study with ethanolic ammonia and 9 - (tetrahydro - 2′ - pyranyl) - 2,6,8 - trichloropurine (IV) at room temperature revealed that in this instance both 8-amino-2,6-dichloro-9-(tetrahydro-2′-pyranyl)purine (X) and 6-amino-2,8-dichloro-9-(tetra-

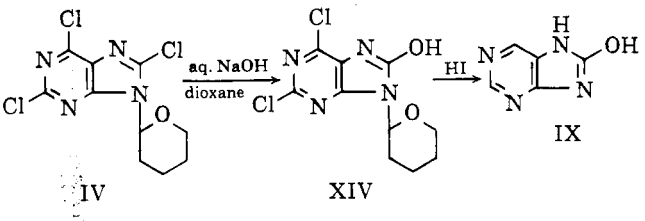
(15) R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis, and A. Jackson, *ibid.*, **83**, 2574 (1961).



SCHEME 2

hydro-2′-pyranyl)purine (XI) were formed. X, however, was obtained in a much greater proportion. The structures of X and XI were established by conversion with hydriodic acid to the known 8-aminopurine[16] and adenine, respectively. Mild acid hydrolysis provided the previously unknown 8-amino-2,6-dichloropurine (XII). The reaction of ammonia and 2,6,8-trichloropurine directly yields 6-amino-2,8-dichloropurine.[2] As expected, IV and excess sodium sulfide at room temperature gave 2-chloro-9-(tetrahydro-2′-pyranyl)-6,8-purinedithiol (XIII). The structure of XIII was established by treatment with Raney nickel in refluxing 2-ethoxyethanol. At this temperature the pyran and mercapto groups were removed simultaneously to yield 2-chloropurine.[17]

When 9-(tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV) was treated with dilute aqueous sodium hydroxide in dioxane at room temperature, only the chlorine at position 8 was removed to yield 2,6-dichloro-8-hydroxy-9-(tetrahydro-2′-pyranyl)purine (XIV). The structure of XIV was determined by its



conversion to 8-hydroxypurine (IX) with hydriodic acid.

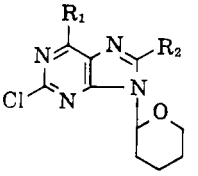
Further indication of the stabilizing effect of anion formation in the imidazole ring is found in the fact that 8-chloropurine[18] is extremely stable to base. Four normal boiling sodium hydroxide and 8-chloropurine gave unchanged starting material after one hour and forty-five minutes.[18] In contrast, 6-chloropurine is reported to yield hypoxanthine in the presence of boiling 0.1 *N* sodium hydroxide.[19]

It is of considerable interest that in the case of 6,8-dichloropurine, thiourea in refluxing ethanol gives 6,8-purinedithiol.[14] Similarly, Ballweg[7] has reported that

(16) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).
(17) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).
(18) A. G. Beaman and R. K. Robins, *J. Appl. Chem.*, **12**, 432 (1962).
(19) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Am. Chem. Soc.*, **76**, 6073 (1954).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF 9-(TETRAHYDRO-2′-PYRANYL) PURINES

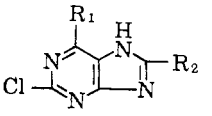


Compound no.	R_1	R_2	pH 1 λ_{max} mμ	pH 1 ε	pH 11 λ_{max} mμ	pH 11 ε
IV	Cl	Cl	279	12,600	282.5	11,400
V	C_2H_5O	C_2H_5O	267	14,100	266	14,900
VI	Cl	C_2H_5O	251	4,590	251	7,350
			281.5	12,000	280.5	12,800
X	Cl	NH_2	243	6,200	226.5	10,200
			289.5	13,800	265	7,480
					299.5	11,800
XI	NH_2	Cl	267.5	15,200	268	16,400
			275[a]	12,900		
XIII	SH	SH	275	6,750	267	15,900
			362.5	17,600	342	18,500
XIV	Cl	OH	249.5	6,550	229.5	13,100
			289	13,700	270	10,100
					302	13,000

[a] Inflection.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF VARIOUS PURINES



Compound no.	R_1	R_2	pH 1 λ_{max} mμ	pH 1 ε	pH 11 λ_{max} mμ	pH 11 ε
VII	C_2H_5O	C_2H_5O	265.5	13,500	274.5	13,800
VIII	Cl	C_2H_5O	282.5	12,300	228.5	14,200
					289	10,700
XII	Cl	NH_2	248.5	4,080	237	16,900
			290	15,900	302	14,300
XV	Cl	*p*-ClC_6H_4NH	299.5	18,900	305.5	28,000

2,6,8-trichloropurine under the same conditions yields 2-chloro-6,8-purinedithiol. In these two instances it is clear that nucleophilic attack occurs without formation of the anion IIIa or IIIb. Thiourea is an example of a good nucleophile but a weak base; therefore, displacement at carbon 8 *does* occur in the absence of a strongly basic nucleophile.

In this regard it is interesting to consider the reaction of 2,6,8-trichloropurine and strong acid. Fischer[2] showed that in the presence of strong acid, reaction occurs at position 8 to give 2,6-dichloro-8-hydroxypurine. Similarly, Robins[14] has shown that under acidic conditions 6,8-dichloropurine yields 6-chloro-8-hydroxypurine. Robins[14] has postulated protonation in the imidazole ring under these conditions, which would greatly lower the electron density at position 8 thus favoring nucleophilic attack at that position.

It is quite probable that in order to obtain good correlation between electron density calculations of nitrogen heterocyclic compounds and laboratory experimental observations, careful examination of the actual species undergoing reaction is a most important factor to be considered. Heterocyclic systems often form ionic species in the reaction media which considerably

change the electron distribution of the isolated molecule. Such a situation has recently been observed[20] for pyrazole and imidazole and is probably quite general for similar heterocycles.

Experimental[21]

2-Chloro-6,8-diethoxy-9-(tetrahydro-2′-pyranyl)purine (V).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 1 g.) was stirred for 3 hr. at room temperature with 15 ml. of ethanol containing 0.23 g. of dissolved sodium. The resulting solution was cooled and filtered. The crude product was washed with water and recrystallized from ethanol to yield 0.9 g. (84.8%) of crystals, m.p. 130–131°.

Anal. Calcd. for $C_{14}H_{19}ClN_4O_3$: C, 51.3; H, 5.8; N, 17.1. Found: C, 51.3; H, 6.1; N, 17.2.

9-Methyl-2,6,8-trichloropurine (II).—Anhydrous 2,6,8-trichloropurine[6] (86 g.), 102 g. of methyl iodide, 54.4 g. of anhydrous potassium carbonate, and 3800 ml. of dimethyl sulfoxide were stirred mechanically at room temperature for 24 hr. At the end of this period 1000 g. of ice was added and precipitation occurred. The white solid was filtered, washed with ice–water, and dried to yield 45 g. of crude product, m.p. 168.5–176°. Two recrystallizations from ethanol gave 29 g. of white crystalline needles, m.p. 176–176.5° (lit.[9] m.p. 176.5°). Ultraviolet absorption data: $\lambda_{max}^{pH\ 1}$, 279 mμ, ε 18,100; $\lambda_{max}^{pH\ 11}$, 280.5 mμ, ε 17,800; λ_{max}^{EtOH} 280 mμ, ε 17,500.

Anal. Calcd. for $C_6H_3Cl_3N_4$: C, 30.3; H, 1.3; N, 23.5. Found: C, 30.5; H, 1.5; N, 23.8.

7-Methyl-2,6,8-trichloropurine (I).—8-Chlorotheobromine[22] (44 g.) and 540 ml. of phosphorus oxychloride were refluxed for 24 hr. The excess phosphorus oxychloride was removed under reduced pressure, employing a steam bath as a source of heat, until the rate of distillation slowed down to a few drops per second. The residue was then poured onto 1000 g. of an ice and water mixture and the suspension allowed to stand for 15 min. with occasional stirring. The product was then filtered, washed with water to remove the acid, and finally washed with ethanol to give 17 g. of a yellow-white solid. Recrystallization of the crude product from ethanol gave 9.6 g. (19.7%) of long, slender white needles, m.p. 158.5–160.5° (lit.[9] 159–161°). The acidic filtrate was set aside in the refrigerator for 2 days to yield 20 g. of 8-chlorotheobromine. Ultraviolet absorption data: $\lambda_{max}^{pH\ 1}$, 285 mμ, ε 11,300; $\lambda_{max}^{pH\ 11}$, 285 mμ, ε 10,400; λ_{max}^{EtOH} 284 mμ, ε 10,700.

Anal. Calcd. for $C_6H_3Cl_3N_4$: C, 30.3; H, 1.3; N, 23.5. Found: C, 30.6; H, 1.3; N, 23.8.

2-Chloro-6,8-diethoxypurine (VII).—2-Chloro-6,8-diethoxy-9-(tetrahydro-2′-pyranyl)purine (V, 3 g.) was dissolved in 200 ml. of ethanol. The solution was acidified to pH 1 with 1 *N* hydrochloric acid and allowed to evaporate at room temperature. The residue was washed with water and recrystallized from benzene to yield 1.4 g. (62.8%) of 2-chloro-6,8-diethoxypurine (VII), m.p. 202–204.5°.

Anal. Calcd. for $C_9H_{11}ClN_4O_2$: C, 44.5; H, 4.5; N, 23.1. Found: C, 44.6; H, 4.7; N, 23.3.

2,6-Dichloro-8-ethoxy-9-(tetrahydro-2′-pyranyl)purine (VI).—To ethanol (75 ml.), containing 0.37 g. of dissolved sodium, was added 5.0 g. of 9-(tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV). The solution was stirred for 3 hr. at room temperature, and then 50 g. of ice was added with vigorous stirring. The resulting precipitate was filtered, washed with water, and dried to yield 4.6 g. of a white solid which was recrystallized from *n*-heptane to yield 3.2 g. of product contaminated with a small amount of 2,8-dichloro-6-ethoxy-9-(tetrahydro-2′-pyranyl)purine. This crude product was twice more recrystallized from *n*-heptane to yield 1.18 g. of 2,6-dichloro-8-ethoxy-9-(tetrahydro-2′-pyranyl) purine (VI), m.p. 114–116.5°.

Anal. Calcd. for $C_{12}H_{14}Cl_2N_4O_2$: C, 45.4; H, 4.4; N, 17.7. Found: C, 45.2; H, 4.4; N, 17.6.

The Formation of 6,8-Dihydroxypurine from 2-Chloro-6,8-diethoxy-9-(tetrahydro-2′-pyranyl)purine (V).—2-Chloro-6,8-diethoxy-9-(tetrahydro-2′-pyranyl)purine (V, 1.1 g.) was treated with 22 ml. of 47% hydriodic acid under reflux for 2 hr. The solution was filtered and evaporated to dryness on the steam bath, and 20 ml. of concentrated aqueous ammonia was added to the residue. The solution was then heated on the steam bath for 10 min. and filtered, and the filtrate was acidified to pH 1 with concentrated hydrochloric acid. The precipitated solid was filtered with suction, washed with water, and recrystallized from boiling water to yield 0.3 g. The acidic filtrate was allowed to evaporate at room temperature, and the remaining residue was washed with and recrystallized from water to give 0.1 g. The over-all yield was 0.4 g. (78.3%) of 6,8-dihydroxypurine. The compound gave a negative test for halogen (sodium fusion). The ultraviolet absorption spectra were identical to those of 6,8-dihydroxypurine.[14]

Anal. Calcd. for $C_5H_4N_4O_2$: C, 39.5; H, 2.6; N, 36.8. Found: C, 39.7; H, 2.7; N, 36.8.

9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV).—2,6,8-Trichloropurine[6] (63 g., anhydrous) was dissolved in 400 ml. of ethyl acetate and slowly heated to 35° with stirring. *p*-Toluenesulfonic acid (100 mg.) was then added, followed by dropwise addition of 43 g. of 2,3-dihydro-4*H*-pyran over a 10-min. period. The temperature rose to 55°; the source of heat was removed, and stirring was continued for another 15 min. The solution was then rapidly cooled to room temperature and extracted with four 25-ml. portions of aqueous (saturated) sodium carbonate, followed by washing with five 25-ml. portions of water until the solution was neutral. The resulting solution was dried over anhydrous sodium sulfate for 5 hr. and filtered, and the excess ethyl acetate was evaporated at 50° under reduced pressure. The resulting solid was recrystallized from *n*-heptane to yield 52.5 g. (60.8%) of a white crystalline solid, m.p. 117–119°.

Anal. Calcd. for $C_{10}H_9Cl_3N_4O$: C, 39.1; H, 2.9; N, 18.2. Found: C, 38.8; H, 3.1; N, 18.0.

2,6-Dichloro-8-ethoxypurine (VIII).—2,6-Dichloro-8-ethoxy-9-(tetrahydro-2′-pyranyl)purine (VI, 208 mg.) was dissolved in ethanol to which was added 2 drops of 1 *N* hydrochloric acid. The solution was allowed to evaporate at room temperature, and the residue was washed with water and recrystallized from benzene to yield 2,6-dichloro-8-ethoxypurine (VIII), m.p. 194.5–196°.

Anal. Calcd. for $C_7H_6Cl_2N_4O$: C, 36.1; H, 2.6; N, 24.1. Found: C, 36.2; H, 2.4; N, 24.1.

The Formation of 8-Hydroxypurine (IX) from VI.—2,6-Dichloro-8-ethoxy-9-(tetrahydro-2′-pyranyl)purine (VI, 300 mg.) was treated with 10 ml. of 47% hydriodic acid under reflux for 2 hr. The solution was filtered and evaporated to dryness on the steam bath. Water (5 ml.) was added to the residue; the pH was adjusted to 11 with 4 *N* sodium hydroxide, and the solution was filtered. The ultraviolet absorption spectra of the filtrate showed only 8-hydroxypurine. R_f values in solvents A, B, and D were identical to those of an authentic sample of 8-hydroxypurine.[23]

8-Amino-2,6-dichloro-9-(tetrahydro-2′-pyranyl)purine (X) and 6-Amino-2,8-dichloro-9-(tetrahydro-2′-pyranyl)purine (XI).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 3 g.) in 120 ml. of ethanolic ammonia (saturated at 0°) was stirred for 3 hr. at room temperature in a closed container. The resulting mixture was filtered and the crude product washed with water and recrystallized from water and ethanol to yield 1.95 g. (69.5%) of 8-amino-2,6-dichloro-9-(tetrahydro-2′-pyranyl)purine (X), m.p. > 300°.

Anal. Calcd. for $C_{10}H_{11}Cl_2N_5O$: C, 41.7; H, 3.8; N, 24.3. Found: C, 41.5; H, 4.0; N, 24.1.

The filtrate from the above reaction mixture was evaporated and the residue washed with water. The crude product was recrystallized from ethanol to yield 0.7 g. (24.9%) of 6-amino-2,8-dichloro-9-(tetrahydro-2′-pyranyl)purine (XI), m.p. > 300°.

Anal. Calcd. for $C_{10}H_{11}Cl_2N_5O$: C, 41.7; H, 3.8; N, 24.3. Found: C, 41.8; H, 4.0; N, 24.0.

Treatment of X and XI with hydriodic acid gave only 8-aminopurine and adenine, respectively. No contamination by the other isomer was detected by paper chromatography.

8-Amino-2,6-dichloropurine (XII).—8-Amino-2,6-dichloro-9-(tetrahydro-2′-pyranyl)purine (X, 150 mg.) was dissolved in 100 ml. of ethanol. The solution was acidified to pH 1 with 1 *N* hydrochloric acid, allowed to stand overnight at room temperature, and then reduced to dryness under reduced pressure. The residue was washed with water and recrystallized from water and methanol to yield 90 mg. (85.0%) of 8-amino-2,6-dichloropurine (XII), m.p. > 300°.

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Anal. Calcd. for $C_5H_3Cl_2N_5$: C, 29.4; H, 1.5; N, 34.3. Found: C, 29.4; H, 1.3; N, 33.7.

Reduction of 2-Chloro-6,8-dimercapto-9-(tetrahydro-2′-pyranyl)purine (XIII) with Raney Nickel to Yield 2-Chloropurine.—2-Chloro-6,8-dimercapto-9-(tetrahydro-2′-pyranyl)purine (XIII, 250 mg.) was dissolved in 40 ml. of 2-ethoxyethanol to which was added 3 g. of Raney nickel, and the solution was refluxed for 2 hr. The ultraviolet absorption spectra and paper chromatographic data in solvents A, B, and C run on the filtrate of the reaction mixture showed 2-chloropurine[16] as the only purine derivative present.

2-Chloro-6,8-dimercapto-9-(tetrahydro-2′-pyranyl)purine (XIII).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 1 g.) was added to 1.03 g. of sodium sulfide (containing 2.7 mole equivalents of water) in 15 ml. of ethanol. The solution was stirred for 3 hr. at room temperature; the mixture was then filtered and the ethanol evaporated at 50° under reduced pressure. The yellow, gummy product was similarly evaporated several times with 50 ml. of benzene until a powdery solid remained. This substance was then dissolved in benzene and methanol, treated with charcoal, filtered, and evaporated to dryness to yield 0.95 g. (96.7%) of a yellow powder, m.p. > 300°.

Anal. Calcd. for $C_{10}H_{11}ClN_4OS_2$: C, 39.6; H, 3.6; N, 18.5. Found: C, 39.7; H, 3.3; N, 18.5.

2,6-Dichloro-8-hydroxy-9-(tetrahydro-2′-pyranyl)purine (XIV).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 5 g.) was dissolved in 500 ml. of anhydrous *p*-dioxane containing 48.8 ml. of 0.9965 *N* sodium hydroxide. The solution was stirred for 22 hr. at room temperature, and the excess *p*-dioxane was removed under vacuum. Water was added to the residue, and a small amount of precipitate which formed was filtered. The filtrate was acidified to pH 1 with 1 *N* hydrochloric acid, and the solid that appeared was filtered, triturated, and washed with water, and dried to yield 2.0 g. (42.6%) of a pure white powder, m.p. > 300°, which could not be recrystallized successfully.

Anal. Calcd. for $C_{10}H_{10}Cl_2N_4O_2$: C, 41.5; H, 3.5; N, 19.4. Found: C, 41.3; H, 3.7; N, 19.5.

Hydrolysis of XV with hydriodic acid as for VI gave 8-hydroxypurine identified by ultraviolet absorption spectra and R_f values in solvents[24] A, B, and D.

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(24) Solvent A, *i*-PrOH:H_2O::6:4—descending; B, *n*-BuOH:H_2O:HOAc (glacial)::5:4:1—descending; C, *n*-BuOH saturated with H_2O plus 1% NH_4OH—descending; D, *i*-PrOH:DMF:NH_4OH::65:25:10—descending; E, 5% NH_4HCO_3 in H_2O—descending; F, 5% Na_2HPO_4 in H_2O saturated with isoamyl alcohol—descending; G, *n*-BuOH saturated with H_2O—descending; H, EtOH:H_2O::7:3—ascending; I, *n*-BuOH:H_2O:HOAc (glacial)::5:4:1—ascending; J, $(NH_4)_2SO_4$:1 *N* NaOAc:*i*-PrOH::40:9:1—ascending.

Aromatic Fluorine Compounds. XI. Replacement of Chlorine by Fluorine in Halopyridines

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The α-halogenated pyridines react with potassium fluoride in various solvents to give replacement of the α-halogen by fluorine. A 50% yield of 2-fluoropyridine was obtained from 2-chloropyridine by heating with potassium fluoride in dimethyl sulfone or tetramethylene sulfone for twenty-one days; 2-bromopyridine gave a similar yield with a heating period of only seven days. The α-halogens of the polyhalopyridines undergo the exchange reaction more readily than do the halogens of the α-monohalopyridines. The proposed structures of the fluoropyridines are supported by alternate syntheses and by n.m.r. studies.

It previously has been found by Finger and coworkers that chlorine in certain positions in polychlorobenzenes[5] can be replaced by fluorine using the potassium fluoride exchange reaction. For example, hexachlorobenzene will react with potassium fluoride to give 1,3,5-trichloro-2,4,6-trifluorobenzene as a major product,[5] and small amounts of dichlorotetrafluorobenzene and chloropentafluorobenzene.[6] This shows that chlorine is not only a strong activating group from the *meta* position as expected in nucleophilic reactions,[7] but is also a significant activator even from the *ortho* and *para* positions.

In this study halogen activation has been demonstrated also in the polychloropyridines. A second halogen atom (chlorine or bromine) either adjacent to or opposite an α-chlorine on the pyridine ring gives increased lability to atoms in the α-position for reaction with potassium fluoride. These findings make it possible to synthesize many fluoropyridines more simply than can be done by the multi-step Schiemann operations.

Several years ago in the early stages of this study progress was slow with the reaction media then in use,[8] until it was discovered that dimethyl sulfone[9] was a better solvent medium for many exchange reactions. Unfortunately early work with 2-chloropyridine[9-11] and potassium fluoride led to the belief that activation by a ring nitrogen alone was insufficient for an exchange reaction; however, it has now been established that on prolonged heating 2-fluoropyridine (I) can be obtained in a significant yield. For instance, heating a mixture of 2-chloropyridine and potassium fluoride in dimethyl sulfone for twenty-one days gave a 50% yield of 2-fluoropyridine.[12] 2-Bromopyridine in dimethyl sulfone

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