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Studies of Purine *N*-Oxides. II. The Reaction of Hypoxanthine 1-*N*-Oxide and 2′, 3′, 5′-Tri-*O*-acetylinosine 1-*N*-Oxide with Phosphoryl Chloride[1]

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Hypoxanthine 1-*N*-oxide was treated with phosphoryl chloride in the presence of organic bases to give 2, 6-dichloropurine. Adenosine 1-*N*-oxide was converted to inosine 1-*N*-oxide by deamination with nitrous acid. Inosine 1-*N*-oxide was acetylated with acetic anhydride in pyridine to yield 2′, 3′, 5′-tri-*O*-acetylinosine 1-*N*-oxide. The latter compound was similarly converted to 9-(2′ 3′, 5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2, 6-dichloropurine by treating it with phosphoryl chloride in the presence of organic bases.

N-Oxides of various nitrogen-containing heteroaromatic compounds, such as those of pyridine,[2] quinoline[3] and pyrazine[4] derivatives, have been found to be convertible to the corresponding chlorine substituted derivatives by treatment with phosphoryl chloride. 1-*H*-Imidazo[4, 5-*c*]pyridine 5-*N*-oxide (3-deazapurine 1-*N*-oxide) was converted to 4-chloro-1-*H*-imidazo[4, 5-*c*]pyridine by a similar procedure.[5]

Up to the present, however, there has been no report on the introduction of a chlorine atom to a purine derivative by treating the corresponding *N*-oxide with phosphoryl chloride.

Adenine 1-*N*-oxide (I)[6,7] and hypoxanthine 1-*N*-oxide (II)[1,8,9] were treated with phosphoryl chloride, but no change occurred in either case.

It has been found that the presence of an organic base, such as *N*, *N*-dimethylaniline, is necessary for the chlorination of hypoxanthine to 6-chloropurine with phosphoryl chloride.[10]

With this in mind, hypoxanthine 1-*N*-oxide (II) was treated with phosphoryl chloride in the presence of *N*, *N*-dimethylaniline in order to obtain 6-chloropurine 1-*N*-oxide (III), but it was found to be converted to 2, 6-dichloropurine (IV) instead. In spite of all our efforts, the intermediate (III) could not be detected in the same reaction mixture. From this result it may be considered that substitution by the chloride anion occurs readily at the C_2 position of the assumed intermediate III, since

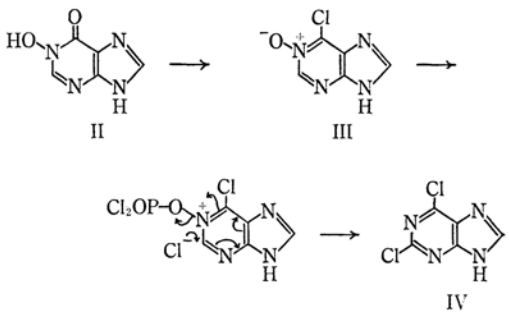

Fig. 1

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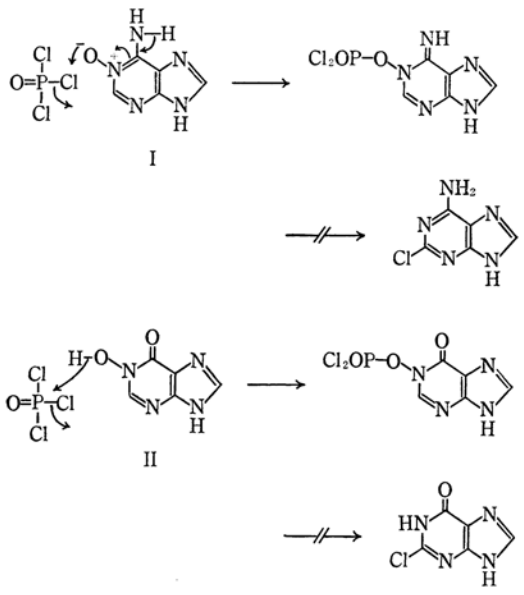

Fig. 2

the pseudoaromaticity in the pyrimidine portion of III increases and consequently leads to the increase in electrophilicity at the C_2 position shown in Fig. 1.

In the case of adenine 1-*N*-oxide (I), however, the postulated dichlorophosphoryl intermediate may be unfavorable for the electron migration which is indispensable for the increase of electrophilicity at C_2 position. In the case of hypoxanthine 1-*N*-oxide, the similar explanation is also applicable in the absence of organic base. (Fig. 2.).

It may be concluded that, prior to the chlorination at the C_2 position, the foregoing formation of 6-chloropurine 1-*N*-oxide occurs. However, more evidence on this point is desirable.

In place of *N*, *N*-dimethylaniline, different organic bases were used. The effects of the bases on the yield of 2, 6-dichloropurine are shown in Table 1.

The effective bases for this reaction vary over a wide range. In the case of tertiary amines, such as triethyl and tripropyl amines, *N*, *N*-dimethylaniline, and nitrogen-containing heteroaromatic compounds, such as 2-picoline, 2-ethylpyridine, 2, 4-, 2, 5- and 2, 6-lutidines, 2, 6-dichloropurine was formed in yields of over 70%. Under the optimum conditions using 2, 6-lutidine, the yield of the product reached nearly 90%. On the other hand, in the case of nitrogen-containing heteroaromatic compounds without any substituent at the α-position, such as 3- and 4-picolines, 3, 4- and 3, 5-lutidines or isoquinoline, no product

TABLE 1. THE EFFECT OF BASES ON THE YIELD OF 2,6-DICHLOROPURINE[a]

Base	m*l*	$POCl_3$ m*l*	Time min	Yield[b] %	pK_a of base[c] (25°C)
Trimethylamine	0.25	6	150	56	9.81
Triethylamine	0.20	6	135	70	10.75
Tri-*n*-propylamine	0.25	7	270	74	
Tri-*n*-butylamine	0.25	3	300	46	9.93
N, *N*-Dimethylaniline	0.25	6	120	66	5.05
Diphenylmethylamine	0.25	6	180	0	
Triphenylamine	0.3(g)	6	300	0	
Diethylamine	0.20	6	240	33	11.04
Cyclohexylamine	0.25	6	240	8.4	10.66
Pyridine	0.25	6	45	34	5.22
2-Picoline	0.25	6	90	83	5.96
3-Picoline	0.25	6	30	0	5.52
4-Picoline	0.25	6	30	0	5.98
2-Ethylpyridine	0.25	6	60	72	5.89
2, 4-Lutidine	0.25	6	120	80	6.63
2, 5-Lutidine	0.25	6	90	67	6.40
2, 6-Lutidine	0.25	6	60	87	6.72
3, 4-Lutidine	0.25	6	40	0	6.46
3, 5-Lutidine	0.25	6	40	0	6.15
2, 4, 6-Colidine	0.25	6	180	28	7.43
Quinoline	0.25	6	180	35	4.81
Isoquinoline	0.25	6	40	0	5.42

a) Hypoxanthine 1-*N*-oxide (0.1 g) was heated in phosphoryl chloride under refluxing.

b) The yield was determined by ultraviolet absorbance (at 277 mμ and 320 mμ) of 0.1 N HCl extract of the excised spot on paperchromatogram. (The solvent system, *n*-butanol - acetic acid - water (4 : 1 : 1, v/v), R_f value: 0.80).

c) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London (1965).

was formed, except pyridine, in which case 2, 6-dichloropurine was obtained in a 30% yield. It is evident from these results that no correlation is to be found between the basicities of the bases employed and the yields of the product. Although final proof is still lacking, a certain degree of steric hindrance around the basic center is probably required in this reaction.

A similar method was applied to 2′, 3′, 5′-tri-*O*-acetylinosine 1-*N*-oxide (VII). Inosine 1-*N*-oxide (VI) has been synthesized by the deamination of adenosine 1-*N*-oxide (V) with nitrosyl chloride,[11] or sodium nitrite in aqueous acetic acid.[9] In this work adenosine 1-*N*-oxide was deaminated with sodium nitrite and aqueous acetic acid, the resulting inosine 1-*N*-oxide (VI) was then isolated in quite a good yield by using cation exchange resin Amberlite IR-120 (H^+ type). The acetylation of inosine 1-*N*-oxide (VI) with acetic anhydride in pyridine gave 2′, 3′, 5′-tri-*O*-acetylinosine 1-*N*-oxide (VII). VII was treated with phosphoryl chloride in the presence of 2-picoline to yield 9-(2′, 3′, 5′-tri-*O*-acetyl-β-D-ribofuranosyl)-2, 6-dichloropurine (VIII).

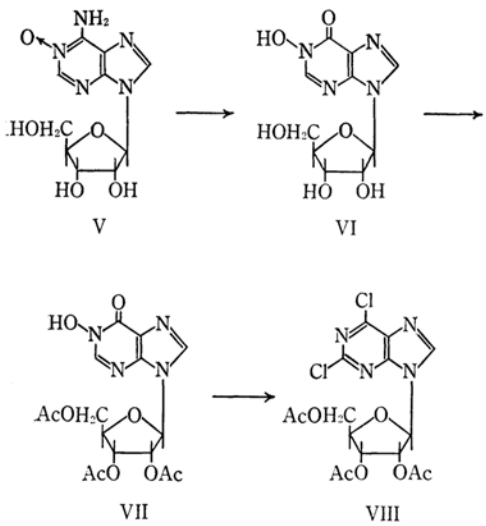

Fig. 3

Experimental

2, 6-Dichloropurine (IV). Hypoxanthine 1-*N*-oxide (1.0 g) was suspended in the mixture of 60 m*l* of phosphoryl chloride and 2 m*l* of triethylamine, and refluxed for 3 hr. After the mixture then been cooled, the excess phosphoryl chloride was distilled off under reduced pressure. The glassy residue was dissolved in 100 m*l* of water, and the product was continuously extracted with ether for 12 hr. From the ether extract the solvent was evaporated to yield 0.8 g of crude 2, 6-dichloropurine, which was crystallized from water to give 0.69 g of pure crystals (54%), mp 177°C.

Found: C, 31.77; H, 1.23; N, 29.67; Cl, 37.4%. Calcd for $C_5H_2N_4Cl_2$: C, 31.77; H, 1.07; N, 29.64; Cl, 37.5%.

Inosine 1-*N*-Oxide (VI). A solution of 24 g of sodium nitrite in 50 m*l* of water was added to a solution of 10 g of adenosine 1-*N*-oxide in 100 m*l* of glacial acetic acid and 200 m*l* of water, and then left to stand at room temperature for two days. The volatile materials were removed from the reaction mixture at 30°C under reduced pressure. The residual solid was dissolved in 100 m*l* of water, passed through a column packed with 300 m*l* of Amberlite IR-120 (H^+ type), and eluted with water. The first 650-m*l* portion of the effluent was discarded, the next 7 *l* of the solution were evaporated to dryness under reduced pressure to give 5.6 g of a light-yellow solid of inosine 1-*N*-oxide (56%). Four grams of colorless crystals were obtained by recrystallization from 90% ethanol. They darkened above 200°C.

Found: C, 42.34; H, 4.48; N, 19.66%. Calcd for $C_{10}H_{12}N_4O_6$: C, 42.25; H, 4.26; N, 19.71%.

2′, 3′, 5′-Tri-*O*-acetylinosine 1-*N*-Oxide (VII). Inosine 1-*N*-oxide (5.0 g) was added to a mixture of 100 m*l* of pyridine and 50 m*l* of acetic anhydride, and the solution was placed in a refrigerator. After two days the reaction mixture was poured into 200 m*l* of ice water. From the aqueous mixture acetic acid, pyridine and a product (VII) were extracted with chloroform, the chloroform layer was washed with a 5% sodium hydrogen carbonate solution and then water to remove acetic acid. The chloroform layer was dried with sodium sulfate, and the chloroform and pyridine were evaporated under reduced pressure. The resulting glassy residue was crystallized by trituration with ethanol. The crude product (6 g, 83%) was recrystallized from ethanol to give fine colorless crystals (4.6 g), mp 194.5—195.5°C.

Found: C, 47.05; H, 4.75; N, 13.47%. Calcd for $C_{16}H_{18}N_4O_9$: C, 46.83; H, 4.42; N, 13.66%.

9-(2′, 3′, 5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-2, 6-dichloropurine (VIII). 2′, 3′, 5′-Tri-*O*-acetylinosine 1-*N*-oxide (1.0 g) was added to a mixture of 24 m*l* of phosphoryl chloride and 1 m*l* of 2-picoline, and the mixture was refluxed for 2 hr. After the excess phosphoryl chloride had been removed by distillation under reduced pressure, the resulting residue was dissolved in 100 m*l* of chloroform and washed with a 5% sodium hydrogen carbonate solution and then water. The chloroform layer was dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The resultant oily residue was crystallized by trituration with ethanol. The light-red crystalline product (0.75 g, 70%) was recrystallized from ethanol to give fine colorless crystals, mp 160—161°C.

Found: C, 43.19; H, 3.78; N, 12.28; Cl, 15.71%. Calcd for $C_{16}H_{16}N_4O_7Cl_2$: C, 42.96; H, 3.61; N, 12.53; Cl, 15.86%.

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