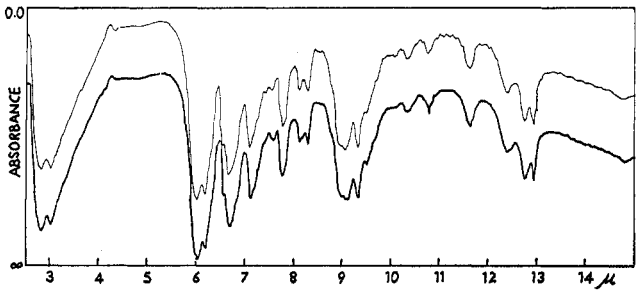


Figure 1.—The infrared spectrum of C-substance. Heavy line = synthetic sample; thin line = sample derived from Gougerotin.

$\lambda_{min}^{0.1\ N\ NaOH}$ 252 (ε 7500) and 225 mμ (ε 8000); ir λ_{max}^{KBr} 2.7, 2.85, 3.35, 4.69, 5.77, 7.01, 7.84, and 9.10 μ.

Anal. Calcd for $C_{10}H_{12}N_6O_6$: C, 38.46; H, 3.87; N, 26.72. Found: C, 38.56; H, 3.81; N, 26.85.

1-(4-Amino-4-deoxy-β-D-glucopyranosyluronic acid)cytosine (C-Substance).—The above nucleoside **15** (96 mg) was dissolved in boiling water (20 ml). The solution was cooled to room temperature and then shaken in a hydrogen atmosphere for 2 hr with 10% palladium on charcoal catalyst (49 mg). The catalyst was filtered and the filtrate was evaporated to dryness to give a quantitative yield (88 mg) of synthetic C-substance as colorless, long needles. Recrystallization from water gave an analytical sample with the following properties: mp 235° dec; $[\alpha]^{25}D$ +6° (*c* 0.89, water) [lit.[15] mp 235° dec, $[\alpha]^{20}D$ +2° (water)]. Both the synthetic and the Gougerotin-derived C-substance migrated as a single spot (+6.9 cm) on paper electrophoresis in borate buffer (pH 9.2, 800 V, 4 hr). The infrared spectra of both samples were identical (see Figure 1), as were also their ultraviolet spectral characteristics. A mixture melting (decomposition) point showed no depression.

Anal. Calcd for $C_{10}H_{14}N_4O_6 \cdot {}^1/_2H_2O$: C, 40.68; H, 5.08; N, 18.98. Found: C, 40.70; H, 5.10; N, 18.88.

The nmr spectrum of the analytical sample showed the presence of 0.5 mol of water of crystallization.

Registry No.—**3**, 22176-09-6; **4**, 22176-10-9; **5**, 22176-11-0; **6**, 22176-12-1; **7**, 22212-28-8; **8**, 22176-13-2; **9**, 21209-53-0; **10**, 22176-15-4; **11**, 22176-16-5; **12**, 22176-17-6; **13**, 22176-18-7; **15**, 22176-19-8; C-substance, 22176-20-1.

Acknowledgment.—The authors are indebted to Mr. Marvin J. Olsen for the nmr spectra on a Varian A-60 and to Dr. S. Tatsuoka of Takeda Chemical Industries, Osaka, Japan, for a sample of Gougerotin.

Pyrrolopyrimidine Nucleosides. V. A Study on the Relative Chemical Reactivity of the 5-Cyano Group of the Nucleoside Antibiotic Toyocamycin and Desaminotoyocamycin. The Synthesis of Analogs of Sangivamycin[1]

BARBARA C. HINSHAW, JOHN F. GERSTER, ROLAND K. ROBINS, AND LEROY B. TOWNSEND

Department of Chemistry and Department of Biopharmaceutical Sciences, University of Utah, Salt Lake City, Utah 84112

Received June 13, 1969

A study of the pyrrolo[2,3-*d*]pyrimidine ring system has revealed that a substituent residing in the pyrimidine ring has a pronounced effect on the reactivity of a cyano group in the pyrrole moiety. It was found that a group (keto) capable of supporting an anion at position 4 decreased the reactivity of the cyano group at position 5 toward nucleophilic attack in comparison to a group (amino) at position 4 incapable of supporting an anion. The reactivity of the cyano groups described above appears to be reversed under acidic conditions. This study has furnished a number of 4,5-disubstituted 7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidines with carboxamido-type groups (amidoxime, amidrazone, thiocarboxamide) at position 5. These derivatives which contain an amino group at position 4 may be considered as analogs of the nucleoside antibiotic sangivamycin.

A recent investigation[2-4] on the reactivity of the pyrrolo[2,3-*d*]pyrimidine ring system toward electrophilic attack has revealed that the introduction of an electrophile into the pyrrole moiety is dependent to a large extent on the type of substituent already present in the pyrimidine ring. This prompted the present investigation on the possible effect that different substituents in position 4 of the pyrrolo[2,3-*d*]pyrimidine ring might have on the chemical reactivity of a cyano group at position 5. This study was also of considerable interest, since, although both groups are in different rings, they lie in very close proximity.

Toyocamycin[5] [**5**, 4-amino-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine] has an exocyclic amino group at position 4 and a cyano group in the adjacent ring at position 5.

Treatment of toyocamycin (**5**) (Scheme I) with hydrazine at reflux temperature for 2 hr furnished a good yield of 4-amino-7-(β-D-ribofuranosyl)pyrrolo-[2,3-*d*]pyrimidine-5-carboxamidrazone (**7**) as established by pmr, ir, and uv (Table I) spectra and elemental analysis. Therefore, nucleophilic attack at the 5-cyano group had proceeded in the presence of an amino group at position 4, which indicated that the cyano group of toyocamycin was susceptible to nucleophilic attack. This was corroborated by the formation of 4-amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamidoxime (**4**) in 85% yield from **5** on treatment with hydroxylamine. However, the conversion of **5** into 4-amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamidine (**2**) with methanolic ammonia was unsuccessful even under drastic conditions. This established that, although the cyano group of **5** was suscep-

(1) This investigation was supported by Research Contract PH-43-65-1041 with Chemotherapy, National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

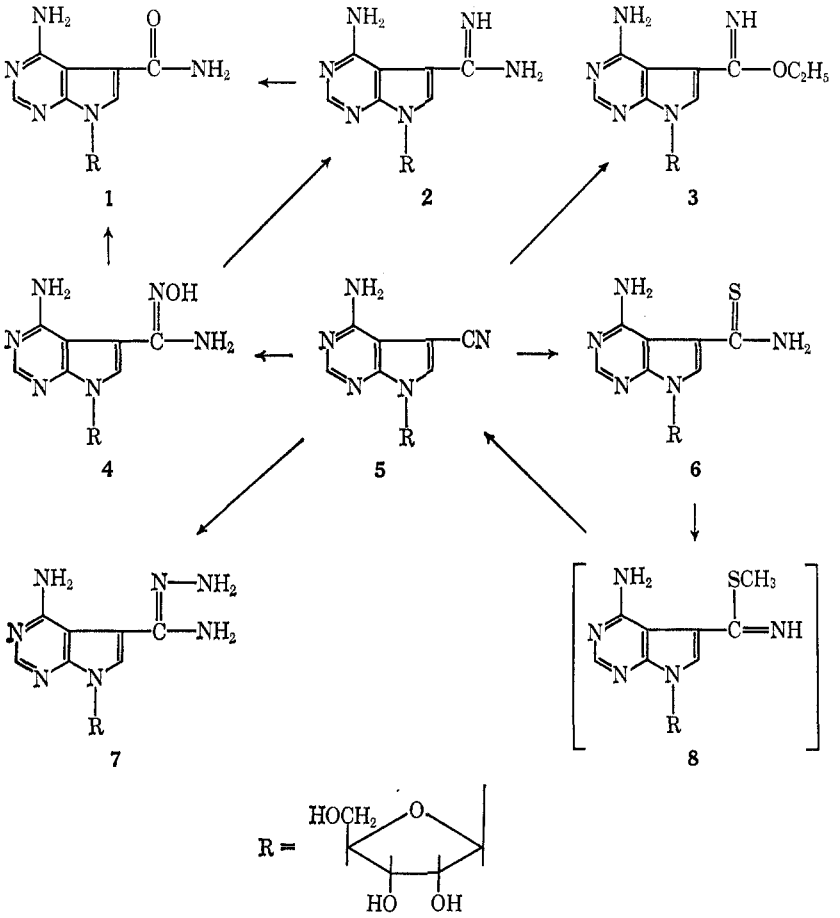
(2) Part of this work has been presented in a preliminary report: L. B. Townsend, B. C. Hinshaw, R. L. Tolman, R. K. Robins, and J. F. Gerster, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., 1968, Abstract MEDI 29.

(3) B. C. Hinshaw, J. F. Gerster, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **6**, 215 (1969).

(4) J. F. Gerster, B. C. Hinshaw, R. K. Robins, and L. B. Townsend, *ibid.*, **6**, 207 (1969).

(5) R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, **91**, 2102 (1969).

SCHEME I



tible toward nucleophilic attack, a strong nucleophile was required. The preparation of **2** was then attempted by a reduction of the carboxamidoxime group of **4** with commercial Raney nickel. However, the reaction was conducted under slightly basic conditions, and, although **2** was presumably formed, a facile hydrolysis occurred to afford the known nucleoside antibiotic sangivamycin[5] (1,4-amino-7-(β-D-ribofuranosyl)pyrrolo-[2,3-*d*]pyrimidine-5-carboxamide) as established by uv spectra, tlc, and mixture melting point. The preparation of **2** was accomplished very readily by the reduction of **4** with palladium on carbon in a hydrogen atmosphere, and in fact it was later found that **2** could be prepared by using thoroughly washed Raney nickel for the reduction. Nucleophilic attack was also observed on treatment of **5** with hydrogen sulfide, triethylamine, and pyridine. This furnished a good yield of 4-amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-pyrimidine-5-thiocarboxamide (**6**, thiosangivamycin) which is structurally very similar to sangivamycin. This nucleoside (**6**) is also of considerable interest from a chemotherapeutic viewpoint, since **6** has demonstrated[6] significant anticancer activity against leukemia L-1210. Several attempts were made to prepare the very reactive methyl 4-amino-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine-5-thioformimidate (**8**) by alkylation of the thioamide group of **6**. However, alkylation occurred only above 10° and was accompanied by methanethiol elimination to afford toyocamycin (**5**).

(6) Unpublished data from the Cancer Chemotherapy National Service Center.

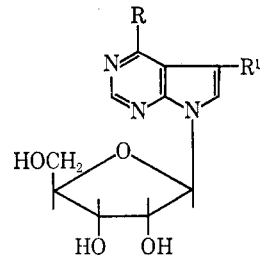
It was assumed[7] that this elimination was the direct result of the basic reaction conditions. This prompted us to investigate the reactivity of the cyano group under acidic conditions. Treatment of **5** with hydrogen chloride in ethanol furnished ethyl 4-amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-formimidate hydrochloride (**3**), but only after prolonged treatment. It was of interest that while toyocamycin (**5**) was soluble in ethanol with basic reagents (nucleophilic attack occurring at the 5-cyano group), it was rather insoluble in acidic ethanol and an extended reaction time was necessary to complete this reaction (formation of **3**). This difference in reactivity under acidic and basic conditions prompted us to determine what effect an enolizable group in the pyrimidine moiety would have on the reactivity of the cyano group in the pyrrole moiety at position 5.

Diazotization of the exocyclic amino group of **5** was accomplished with nitrous acid to afford 5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone (**13**) (Scheme II). In direct contrast with **5**, when **13** was slurried in ethanol and hydrogen chloride gas was slowly passed through the reaction mixture, a facile formation of ethyl 7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-formimidate hydrochloride (**16**) was observed. Although this reaction under acidic conditions proceeded much faster with **13** than the analogous reaction with **5**, it was found that reactions under basic conditions furnished just the opposite results. Treat-

(7) A similar reaction has been previously observed: A. Yamazaki, I. Kumashiro, T. Takenishi, and M. Ikehara, *Chem. Pharm. Bull.* (Tokyo), **16**, 2172 (1968).

TABLE I

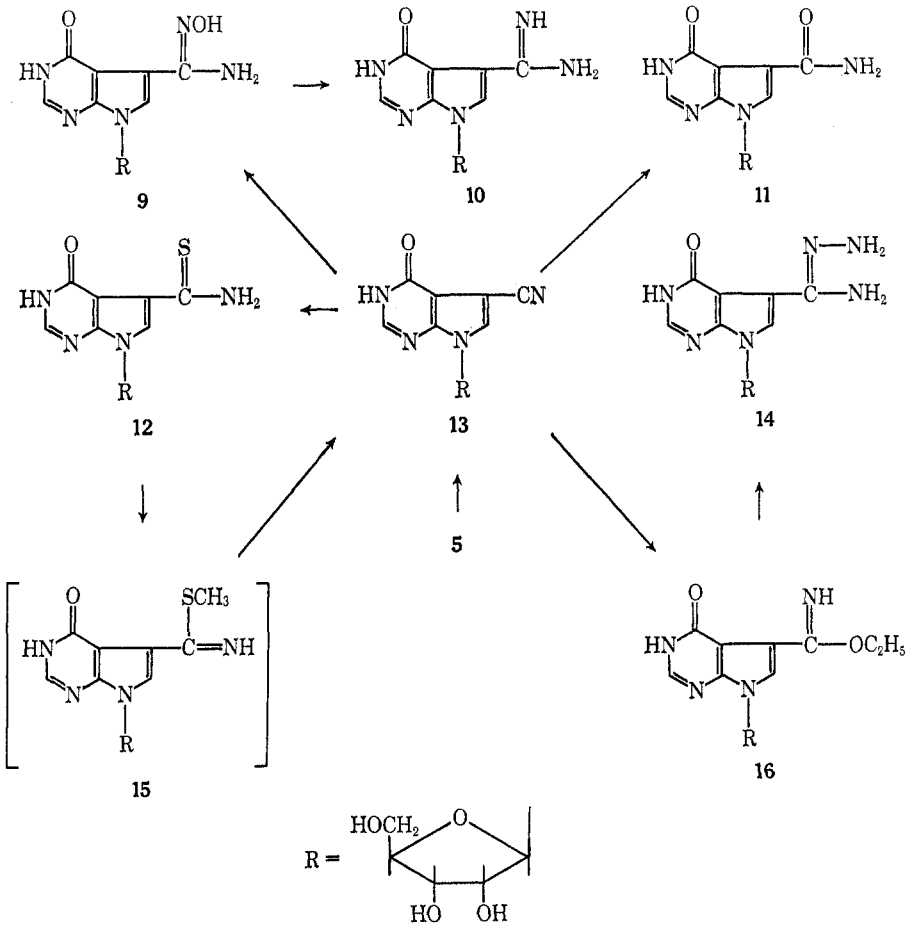
ULTRAVIOLET ABSORPTION SPECTRAL DATA FOR CERTAIN 4,5-DISUBSTITUTED 7-(β-D-RIBOFURANOSYL)PYRROLO[2,3-*d*]PYRIMIDINES[a]



Compd	R	R¹	$\lambda_{max}^{pH\ 1}$, nm	ε	λ_{max}^{EtOH}, nm	ε	$\lambda_{max}^{pH\ 11}$, nm	ε
		S ‖ CNH_2						
6	NH_2		300[b]	11,700	310[b]	11,700	306[b]	9,100
			287	12,300	287	14,000	279	13,000
			240	17,500	247	13,500		
		NOH ‖ CNH_2						
4	NH_2		273	13,300	278	17,700	275	15,100
							225	15,230
		NNH_2 ‖ CNH_2						
7	NH_2		273	13,300	278.5	19,900	277	14,700
					273	19,100	226	13,000
					231.5	14,200		
		NH·HCl ‖ COC_2H_5						
3	NH_2		273	11,400	280	12,700	278	13,800
					235	6,000	234.5	9,000
		NH·2HCl ‖ CNH_2						
2	NH_2		273	15,300	278	16,800	276	16,800
13	OH	CN	263	8,750	264	9,900	273	10,800
							268[b]	10,500
							230	7,450
		NOH ‖ CNH_2						
9	OH		282[b]	9,700	286	9,100	280	13,900
			272	11,050	247	10,300	226	12,800
		O ‖ CNH_2						
11	OH		267	11,000	267	10,800	274	12,850
					295[b]	3,600	230	9,900
		S ‖ CNH_2						
12	OH		322	10,750	324	17,400	328	9,450
			270	13,400	273	21,700	271	16,000
			262	13,200	264	20,900	265[b]	15,300
					252.5	19,100		
					241	18,500		
		NH ‖ CNH_2						
10	OH		273	7,100	278	5,900	276	7,100
					235	7,400	235.5	6,200
		NH·HCl ‖ COC_2H_5						
16	OH		290[b]	9,800	288[b]	4,900	275	13,300
			275	11,300	268	8,800	233	11,100
			245	10,900	237	4,900		
			235	11,400				
		NH ‖H $CNNH_2$						
14	OH		288[b]	13,000	275	14,400	295[b]	7,900
			277.5	14,700	232	14,800	283[b]	12,600
							273	14,500
							230	12,900

[a] Spectra were obtained with a Beckman DK-2 ultraviolet spectrophotometer. [b] Shoulder.

SCHEME II



ment of **13** with hydrogen sulfide, triethylamine, and pyridine under reaction conditions similar to those used for the conversion of **5** to **6** produced no reaction and only starting material was recovered. In fact, this conversion was not successful even at reflux temperature with the above reagents. The preparation of 7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-thiocarboxamide (**12**) required the treatment of **13** with ethanolic sodium sulfide in a sealed vessel at 125°. This tremendous difference in reactivity of the cyano group observed for **5** and **13** must be due to the difference in the pyrimidine moiety. The removal of the proton from the nitrogen at position 3 of **13** under basic conditions could well account for this difference in reactivity. This would lead to a rearrangement of electrons, which would definitely exert a deactivating influence on the cyano group *via* increased electron density. Electronic repulsion of the incoming nucleophile, by the anion in the pyrimidine ring (probably on the oxygen atom), would also affect the reactivity of the cyano group.

Under acidic reaction conditions, the nucleoside **5** is probably protonated at N-3, thus withdrawing electrons from the pyrrole ring owing to the resulting positive charge in the pyrimidine ring. This could account for the difficulty encountered in acid-catalyzed reactions of the cyano group, since protonation of the cyano group would be inhibited by the positive charge already in the system. The keto group of **13** under acidic conditions should not be protonated as readily as the amino group, and thus protonation of the cyano group and reaction with a nucleophile would be more likely to occur. Of consideration also in comparing the reactivity of the cyano group of the 4-amino *vs.* the 4-keto compound in acidic medium is the relative pK_a of the amino compound **5** compared to that of the keto compound **13**. In the purine series, adenosine has a reported[8] pK_a of 3.5, while inosine has a pK_a of 1.2. Extrapolation to the pyrrolo[2,3-*d*]pyrimidine nucleosides would suggest that toyocamycin (**5**) is more readily protonated than desaminotoyocamycin (**13**). Thus, the reduced reactivity of toyocamycin as compared to that of the 4-keto derivative under certain acidic reaction conditions may well be explained by the difference in pK_a.

The preparation of **15** by alkylation of **12** was attempted, but, as was observed previously, there occurred a facile elimination of methanethiol to afford 5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone (**13**) as established by ir and uv spectra (Table I). Although a longer reaction time was required, treatment of **13** with crystalline hydroxylamine furnished a good yield of 7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-carboxamidoxime (**9**). Catalytic reduction of the 5-carboxamidoxime group of **9** was accomplished to afford 7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-carboxamidine (**10**). The preparation of **10** directly from **13** was not successful even under very forcing conditions. The preparation of **14** was accomplished very easily by treatment of **16** with a stoichiometric quantity of hydrazine. The sangiva-

(8) D. B. Dunn and R. H. Hall in "Handbook of Biochemistry, Selected Data for Molecular Biology," The Chemical Rubber Co., H. A. Sober, Ed., 1968, pp G-21, G-35.

mycin analog (**11**) was prepared by treatment of **13** with hydrogen peroxide under basic conditions and the course of this reaction was conveniently monitored by tlc and uv spectroscopy (Table I).

A correlation between the reactivity of the cyano group in the pyrrole ring and the substituent at position four of the pyrimidine ring of the pyrrolo[2,3-*d*]-pyrimidine ring system seems to be very definitive. This difference appears to be a function of the pH at which the reaction is conducted as well as the reagent and reaction conditions employed.

Experimental Section[9]

4-Amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamidrazone (7).—To a solution of 50 ml of ethanol containing 2 ml of 85% hydrazine hydrate was added 1.5 g of toyocamycin[10] (**5**) and the reaction mixture was heated at reflux temperature for 2 hr. The solution was allowed to stand at 5° for 12 hr, and the product was collected by filtration and recrystallized from water to yield 1.2 g (75%) of pure product, mp 242.5–243.5°. No absorption band in the 2250-cm^{-1} region was observed in the infrared spectrum.

Anal. Calcd for $C_{12}H_{17}N_7O_4 \cdot {}^1/_2H_2O$: C, 43.37; H, 5.46; N, 29.51. Found: C, 43.56; H, 5.51; N, 29.20.

4-Amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamidoxime (4).—Toyocamycin (**5**, 1 g) was dissolved in 100 ml of ethanol containing 1 g of hydroxylamine and the resulting solution was heated at reflux temperature for 2 hr. The mixture was cooled to room temperature, and the product was collected by filtration and recrystallized from 60 ml of water to yield 940 mg (85%) of pure **4**, mp 259° dec. The 2250-cm^{-1} region of the infrared spectrum revealed no absorption band.

Anal. Calcd for $C_{12}H_{16}N_6O_5$: C, 44.40; H, 4.97; N, 25.90. Found: C, 44.18; H, 4.90; N, 26.14.

4-Amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamidine (2).—4-Amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-pyrimidine-5-carboxamidoxime (**4**, 500 mg) was dissolved in 100 ml of boiling ethanol and the solution was cooled to 50°. To this solution was added 500 mg of 10% palladium on powdered charcoal and the mixture was cooled to room temperature and hydrogenated at 45 psi and room temperature for 5 hr. The catalyst was removed by filtration through a Celite pad and the pad was washed with 50 ml of boiling water. The combined filtrate and washings were adjusted to pH 5 with concentrated hydrochloric acid and evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to yield 100 mg of **2**, which was dried *in vacuo* over P_2O_5 for 1 hr for analysis; mp 236–237° dec.

Anal. Calcd for $C_{12}H_{16}N_6O_4 \cdot 2HCl$: C, 37.90; H, 4.75; N, 22.00. Found: C, 37.81; H, 5.04; N, 22.05.

Ethyl 4-Amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-formimidate Hydrochloride (3).—Toyocamycin (**5**, 250 mg) was slurried in 25 ml of absolute ethanol, and dry hydrogen chloride gas was bubbled through this mixture for 0.5 hr. The reaction mixture was stirred at room temperature for 6 hr and heated at reflux temperature for 0.5 hr. The ethanol was removed *in vacuo* and the residue was triturated with ethanol which was again removed *in vacuo*. The above procedure was repeated until all excess hydrogen chloride had been removed. Recrystallization of the crude product from ethanol–water afforded 150 mg (52%) of pure **3**, mp 257–258° dec. The characteristic peak for a cyano group was not observed in the infrared spectrum at 2250 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}N_5O_5 \cdot HCl$: C, 45.00; H, 5.38; N, 18.71. Found: C, 45.00; H, 5.37; N, 19.01.

4-Amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (6).—To 125 ml of pyridine containing 1.5 ml of triethylamine was added 2.9 g of toyocamycin (**5**). This solution was stirred at room temperature for 6 hr with continual passage of hydrogen sulfide gas through the solution. The passage of hydrogen sulfide gas was ceased and the dark solution was stirred at room temperature for an additional 18 hr. The pyridine was removed *in vacuo* and the resulting residue was slurried with water several times and evaporated to dryness each time. The solid was washed with acetone and the product was recrystallized from water–ethanol to yield 1.4 g (43%) of pure product, mp 238–240°. There was no peak at 2250 cm^{-1} for the cyano group, but a peak was observed at 1550 cm^{-1} for the –NC=S moiety in the infrared.

Anal. Calcd for $C_{12}H_{15}N_5O_4S$: C, 44.40; H, 4.36; N, 21.60; S, 9.87. Found: C, 44.20; H, 4.78; N, 21.47; S, 9.90.

4-Amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (1, Sangivamycin).—4-Amino-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidine-5-carboxamidoxime (**4**, 250 mg) was dissolved in 50 ml of hot water by the addition of 8 drops of 25% ammonium hydroxide. To this solution was added 2.5 g of Raney nickel in 1.25-g portions at 0.5-hr intervals and the mixture was heated at reflux temperature with continual stirring for 4 hr. The Raney nickel was collected on a Celite pad and washed with four 10-ml portions of boiling water. When the filtrate was cooled, a solid crystallized and was recrystallized from water to yield 150 mg (63%) of pure product, mp 265–266° dec.

Anal. Calcd for $C_{12}H_{15}N_5O_5$: C, 46.60; H, 4.90; N, 22.60. Found: C, 46.81; H, 4.90; N, 22.35.

5-Cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone (13).—To a warm (55°) solution of 400 ml of water and 26 ml of glacial acetic acid was added 6 g of toyocamycin (**5**). To this solution was added 5 g of sodium nitrite at 0.5-hr intervals until 10 g of sodium nitrite had been added. The solution was then heated at 70° for an additional 1 hr, after which time the water was removed *in vacuo*. The resulting slurry was allowed to form an azeotrope several times with 2-propanol to remove the excess acetic acid. The resulting solid was dissolved in 50 ml of water and allowed to stand for 4–6 days at 25° to give a crude yield of 4.35 g. For analysis, the solid was recrystallized three times from water and dried for 1 hr at 110° over P_2O_5 at 0.1 mm pressure to yield 2.6 g (42%) of **13**, mp 267–269°. Infrared peaks were observed at 2250 cm^{-1} for the cyano group and at 1675 cm^{-1} for the C=O moiety.

Anal. Calcd for $C_{12}H_{12}N_4O_5$: C, 49.30; H, 4.13; N, 19.12. Found: C, 49.50; H, 4.34; N, 19.38.

7-(β-D-Ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-carboxamide (11).[11]—5-Cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone (**13**, 2.0 g) was dissolved in 100 ml of 15% ammonium hydroxide, and two 10-ml portions of 30% hydrogen peroxide were added at 6-hr intervals. The solution was stirred at room temperature for 12 hr, with a total of 20 ml of H_2O_2 being added. The reaction was monitored by thin layer chromatography on SilicAR-7GF using the upper phase of 4:1:2 ethyl acetate–1-propanol–water (v/v). The solution was evaporated under reduced pressure and the residue was recrystallized from methanol–water and dried *in vacuo* to yield 1.34 g (63%) of pure **11**, mp 286–287° dec (lit.[11] mp 290–292°).

Anal. Calcd for $C_{12}H_{14}N_4O_6$: C, 46.40; H, 4.55; N, 18.05. Found: C, 46.27; H, 4.76; N, 17.96.

7-(β-D-Ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-thiocarboxamide (12).—A 200-mg portion of sodium was dissolved in 200 ml of ethanol and hydrogen sulfide gas was passed through this solution for *ca.* 10 min. 5-Cyano-7-(β-D-ribofuranosyl)pyrrolo-[2,3-*d*]-4-pyrimidone (**13**, 1.0 g) was dissolved in 30 ml of ethanol containing 2.5 ml of water, and, after a clear solution had been effected, the solution was added to the sodium hydrosulfide solution, placed in a sealed vessel, and heated at 125° for 6 hr. The crude crystals were collected by filtration and recrystallized from water to yield 550 mg (49%) of pure product, mp 290–291° dec.

Anal. Calcd for $C_{12}H_{14}N_4O_5S$: C, 44.10; H, 4.32; N, 17.15. Found: C, 43.83; H, 4.10; N, 17.27.

7-(β-D-Ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-carboxamidoxime (9).—5-Cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone (**13**, 500 mg) was dissolved in 95 ml of ethanol, and 167 mg of crystalline hydroxylamine[12] was added. The solution was heated at reflux temperature for 4 hr and cooled to room temperature, and the solid (500 mg) was collected by filtration. The solid was recrystallized three times from water and dried at 110° for 1 hr to yield 350 mg (63%) of product, mp 188–191° dec.

Anal. Calcd for $C_{12}H_{15}N_5O_6$: C, 44.30; H, 4.65; N, 21.60. Found: C, 44.39; H, 4.70; N, 21.79.

(9) Infrared spectra were recorded with a Beckman IR-5A spectrophotometer. All melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

(10) Purchased from Koninklijke Nederlandsche Gist-en Spiritusfabriek, N. V., Royal Netherlands Fermentation Industries, Ltd., Delft, Holland, under the name of vengicide.[5]

(11) K. V. Rao, *J. Med. Chem.*, **11**, 939 (1968).

(12) C. D. Hurd, *Inorg. Syn.*, **1**, 87 (1939).

7-(β-D-Ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-carboxamidine (10).—7-(β-D-Ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-carboxamidoxime (**9**, 500 mg) was dissolved in 50 ml of water containing 8 drops of 25% ammonium hydroxide. To this solution was added 2.5 g of commercial Raney nickel, and the reaction mixture was heated at reflux temperature with continuous stirring for 5 hr. The catalyst was removed by filtration through a Celite pad and the Celite pad was washed with four 10-ml portions of boiling water. The product, which had separated from solution when the combined washings and filtrate were cooled to room temperature, was collected by filtration. The product was recrystallized from water to yield 100 mg (21%) of **10**, mp 272° dec.

Anal. Calcd for $C_{12}H_{15}N_5O_5$: C, 46.70; H, 4.90; N, 22.60. Found: C, 46.40; H, 4.93; N, 22.52.

Ethyl 7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-formimidate hydrochloride (16).—5-Cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone (**13**, 500 mg) was slurried in 50 ml of ethanol and dry hydrogen chloride gas was bubbled through this mixture for 0.5 hr with stirring while the reaction mixture was maintained at room temperature. The resulting slurry was evaporated to dryness, ethanol was added, and the slurry was again evaporated to dryness, this process being repeated several times to remove all excess hydrogen chloride. The solid was recrystallized from ethanol and dried for 2 hr *in vacuo* over P_2O_5 to yield 320 mg (55%) of pure product, mp 158–160° (foams). There was no peak observed in the 2250-cm^{-1} region of the infrared spectrum.

Anal. Calcd for $C_{14}H_{18}N_4O_6 \cdot HCl$: C, 45.00; H, 4.84; N, 14.95. Found: C, 45.30; H, 5.01; N, 15.00.

7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-carboxamidrazone (14).—Ethyl 7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-4-pyrimidone-5-formimidate hydrochloride (**16**, 100 mg) was dissolved in 12 ml of ethanol and 0.02 ml of anhydrous hydrazine was then added. A precipitate began to separate from solution after 0.5 hr and the solution was stirred for a total of 5 hr at room temperature. The solvent was removed *in vacuo* and the residue was crystallized from ethanol–water to yield 50 mg (52%), mp 266–274° dec. Recrystallization of this crystalline material from water yielded a small amount of pure compound, which was dried *in vacuo* over P_2O_5 for analysis; mp 264–266°.

Anal. Calcd for $C_{12}H_{16}H_6O_5 \cdot H_2O$: C, 42.20; H, 5.30; N, 24.60. Found: C, 42.75; H, 5.27; N, 24.55.

Registry No.—**1**, 18417-89-5; **2** dihydrochloride, 22242-87-1; **3** hydrochloride, 22242-88-2; **4**, 22242-89-3; **6**, 22242-90-6; **7**, 22242-91-7; **9**, 22242-92-8; **10**, 22242-93-9; **11**, 22242-94-0; **12**, 22242-95-1; **13**, 22242-96-2; **14**, 22242-97-3; **16** hydrochloride, 22242-98-4.

Notes

Synthesis and Cleavage of Phospholane Oxides

B. R. EZZELL[1a] AND LEON D. FREEDMAN[1b]

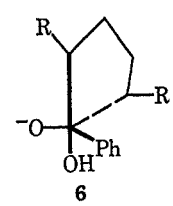
Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27607

Received February 4, 1969

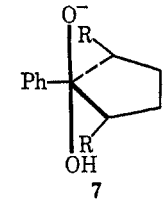
In a recent paper[2] we reported that the heterocyclic ring of the dibenzophosphole 5-oxide system exhibits an unexpected instability toward alkaline cleavage. In contrast to these results, we have now found that the cleavage of two derivatives of 1-phenylphospholane 1-oxide with fused sodium hydroxide obeys the general rule, *viz.*, that the group that is preferentially cleaved is the one capable of forming the more stable carbanion.[3] Hence the phospholane ring *per se* appears to have no decisive influence on which carbon–phosphorus bond is cleaved.

The compounds used in the present study were prepared as shown in Scheme I. It should be noted that Campbell and coworkers[4] reported the formation of **3** under essentially the same conditions that we employed for the preparation of **2**. They reported a melting point of 205–207° for **3**. This value does not agree with our melting point for either **2** (178–180°) or **3** (151–153°). Both of our hydrogenation reactions consumed the calculated amount of hydrogen for reduction to the structures shown in Scheme I. In addition, we obtained elemental analyses and nmr spectra consistent with structures **2** and **3**. That the phenyl group of **2** was attached to phosphorus was unequivocally shown by the fact that fusion with sodium hydroxide (discussed below) produced benzene.

As indicated in Scheme II, fusion of the phospholane oxides **2** and **3** with sodium hydroxide yielded 1-hydroxy-2,5-dicyclohexylphospholane 1-oxide (**4**) and (1,4-diphenylbutyl)phenylphosphinic acid (**5**), respectively. Thus, in both reactions, cleavage occurred so as to form the more stable carbanion. Two structures (**6** and **7**) should be considered for the trigonal-bipyramidal intermediate formed during the reaction of the phospholane oxides with sodium hydroxide.[5] There is less ring strain in **6**, since the heterocyclic ring spans one equatorial and one apical position.[6] However, as we have previously suggested,[2] the formation of intermediates comparable to **6** is probably inhibited because



6



7

(1) (a) Taken from the Ph.D. Dissertation of B. R. E., North Carolina State University, Raleigh, N. C., 1969; (b) to whom inquiries should be addressed.

(2) B. R. Ezzell and L. D. Freedman, *J. Org. Chem.*, **34**, 1777 (1969).

(3) L. Horner, H. Hoffman, and H. G. Wippel, *Chem. Ber.*, **91**, 64 (1958).

(4) I. G. M. Campbell, R. C. Cookson, M. B. Hocking, and A. N. Hughes, *J. Chem. Soc.*, 2184 (1965).

(5) A third possible intermediate having the ring in diequatorial positions and the oxygens in equatorial and apical positions is unlikely for reasons previously discussed.[2]

(6) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).