solid, m.p. 210–217°. Two recrystallizations from 50% aqueous ethanol raised the melting point to 236–239°.

Method C. Raney Nickel in Acetic Acid. Hydrogenation of **3a** (R = H) in acetic acid, as described above, followed by removal of the solvent under reduced pressure, gave a yellow gum which was sublimed at 150° (0.1 mm.). Recrystallization of the sublimate from 50% aqueous ethanol gave **4a** (R = H), m.p. 238–240°, in 69% yield.

Method D. Raney Nickel in Ethanol. Hydrogenation of **3a** (R = H) in ethanol, as described above, followed by removal of the solvent under reduced pressure, gave a pale yellow, semisolid mass. This was stirred with acetic anhydride overnight, the solvent was removed under reduced pressure, and the residual gum was sublimed at 150° (0.1 mm.). Recrystallization of the resulting colorless sublimate from 50% aqueous ethanol gave **4a** (R = H), m.p. 237–240°, in 61% yield.

Method E. Zinc in Acetic Acid. A mixture of 1.0 g. of 2-(2-carboxyethyl)-3(4H)-quinoxalone and 2 g. of zinc dust was stirred in 50 ml. of acetic acid at room temperature for 2 hr. The solid material was filtered off and the acid was removed by distillation under reduced pressure. The residual pale yellow oil and the solids which had been collected by filtration were refluxed for 1 hr. with 50 ml. of acetic anhydride, the hot reaction mixture was filtered free of zinc and zinc acetate, the solvent was distilled off under reduced pressure, and the residual gummy solid was sublimed at 150° (0.1 mm.). The resulting colorless solid (0.5 g., 49%) was recrystallized from 50% aqueous ethanol to give colorless needles, m.p. 235–240°.

Method F. Sodium Borohydride in Sodium Hydroxide. Sodium borohydride (1.0 g.) was added to a solution of 2.0 g. of 2-(2-carboxyethyl)-3(4H)-quinoxalone in 20 ml. of 1 *N* sodium hydroxide and the mixture was allowed to stand at room temperature for 6 hr. Acidification with 6 *N* sulfuric acid gave a clear solution from which the product crystallized as beautiful colorless needles (1.92 g., 98%), m.p. 237–240°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.48; H, 5.07; N, 13.71.

The products obtained by methods A–F were identical, as judged by a comparison of infrared spectra and by mixture melting point determinations.

1,2,3,3a,4,5-Hexahydro-5-methylpyrrolo[1,2-a]quinoxaline-1,4-dione (**4a**, *R* = CH_3). A solution of 2.0 g. of 2-(2-carboxyethyl)-4-methyl-3(4H)-quinoxalone and 1 g. of sodium borohydride in 20 ml. of 1 *N* sodium hydroxide was allowed to stand at room temperature for 6 hr. and then acidified with 6 *N* sulfuric acid. The resulting clear solution deposited 1.88 g. (93%) of beautiful, colorless needles, m.p. 164–168°, upon standing for 1 hr. Recrystallization from aqueous ethanol raised the melting point to 167–169.5°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.52; H, 5.73; N, 13.29.

1,2,3,4,4a,5,6-Heptahydropyridino[1,2-a]quinoxaline-1,5-dione (**4b**, *R* = *H*) was obtained in 78% yield by treatment of 2-(3-carboxypropyl)-3(4H)-quinoxalone (**3b**, R = H) with sodium borohydride as described above. The product crystallized from 50% aqueous ethanol as beautiful, long colorless needles, m.p. 235–237°

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.83; H, 5.67; N, 12.96.

Synthesis of Pyrrolo[2,3-*d*]pyrimidines. The Aglycone of Toyocamycin[1,2]

Edward C. Taylor and Raymond W. Hendess[3]

Contribution from the Department of Chemistry, Princeton University, Princeton, New Jersey. *Received November 16, 1964*

4-Amino-5-cyanopyrrolo[2,3-d]pyrimidine (**2b**), *the aglycone of the antibiotic Toyocamycin, has been prepared from tetracyanoethylene in five steps by reaction with hydrogen sulfide to give 2,5-diamino-3,4-dicyanothiophene* (**4**), *rearrangement with alkali to 2-mercapto-3,4-dicyano-5-aminopyrrole* (**5**), *reaction with trimethyl orthoformate to the methoxymethyleneamino derivative* **6b**, *cyclization with ammonia to 4-amino-5-cyano-6-methylmercaptopyrrolo[2,3-d]pyrimidine* (**8b**), *and finally desulfurization with Raney nickel. 4-Aminopyrrolo[2,3-d]pyrimidine* (**1b**), *the aglycone of the antibiotic Tubercidin, has been prepared from* **2b** *by acid hydrolysis of the cyano grouping to the corresponding 5-carboxylic acid* **11b**, *followed by decarboxylation. Ribosidation of the aglycone* **2b** *via its chloromercury salt gave what is believed to be the 1-ribosyl derivative rather than Toyocamycin itself (the 7-ribosyl derivative). A number of structural analogs of the aglycones* (**1b** *and* **2b**) *of Tubericidin and Toyocamycin, differing from the natural products in possessing a substituted 4-amino group, or alkyl or aryl groups in position 5, were prepared from the 2-amino-3-cyano-4-substituted pyrroles* **15** *and* **16** *by reaction with triethyl orthoformate to give the 2-ethoxymethylenamino derivatives* **17** *and* **18**, *conversion to the formamidines* **19–23** *with amines, cyclization to pyrrolo[2,3-d]pyrimidines* **24–28** *with sodium methoxide in methanol, and rearrangement of the 3-substituted 4-imino derivatives* **26–28** *with boiling water to their aromatic isomers* **29–31**.

(1) This work was supported in part by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

(2) A preliminary report of this work has appeared; E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.*, **86**, 951 (1964).

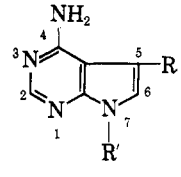
(3) National Institutes of Health Predoctoral Fellow, 1961–1964.

The search for purine analogs which might exhibit antitumor activity because of interference with the synthesis of the naturally occurring purines, or with their utilization in nucleic acid biosynthesis, has been divided broadly into two areas: (1) variation in the nature and position of substituents on the intact purine ring, and (2) modification of the ring system itself, usually by replacement of a methine (CH=) group by nitrogen (N=), or by the preparation of isomeric heterocyclic systems in which the positions of carbon and nitrogen atoms have been reshuffled.

The first area has been extensively investigated and has been the subject of a recent review.[4] Most of the research in the second area has been concerned with the preparation of various azapurines, of which 8-azaguanine and 2- and 8-azaadenine have been of particular interest.[5] Heterocyclic systems isomeric with the purines have likewise been the subject of considerable recent study; the pyrazolo[3,4-*d*]pyrimidine system, and in particular its 4-amino derivative, deserves special mention.[4]

On the other hand, deazapurines have received scant attention. It is worthy of note that although several 7-deazapurines (pyrrolo[2,3-*d*]pyrimidines) were synthesized as early as 1911,[6-9] the first systematic investigations of derivatives of this ring system as potential purine antagonists were reported in 1959–1960.[10,11]

Nature has been more perspicacious than the organic chemist in the design of an effective purine antagonist through this latter type of structural modification. The antibiotic Viomycin has recently been shown by Johnson and co-workers[12] to be a dihydro derivative of a 9-deazapurine. Furthermore, the isolation of two new antibiotics, Tubercidin and Toyocamycin, and their identification as derivatives of the isomeric 7-deazapurine ring system, underscore the effectiveness of such structural modifications on biological activity. Tubercidin, first isolated by Anzai, Nakamura, and Suzuki,[13] was shown to possess structure **1a** on the



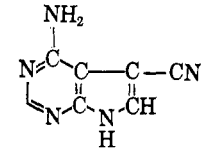
1a, R = H; R′ = β-D-ribose
1b, R = R′ = H
2a, R = CN; R′ = D-ribose
2b, R = CN; R′ = H

basis of degradation studies[14-17] which led to the known 4-aminopyrrolo[2,3-*d*]pyrimidine (**1b**).[11] It is active against *Mycobacterium tuberculosis* BCG and *Candida albicans* and is reported to have strong antitumor activity.[13] It has been demonstrated recently that Tubercidin is incorporated by the cell into both RNA and DNA (as its deoxyriboside, which is formed from Tubercidin by the cell) with the dramatic and lethal consequence that RNA, DNA, and protein synthesis all cease.[18] Toyocamycin, isolated in crystalline form from a species of *Streptomyces*[19] and from the soil near Fuji City, Shizuoka Prefecture,[20] is reported to be active against *M. tuberculosis* $H_{37}R_V$ and against *C. albicans*.[19] Toyocamycin appears to be some fivefold more effective than Tubercidin in inhibiting cell growth.[18] It has been shown to have structure **2a** on the basis of spectral evidence and degradation.[20,21]

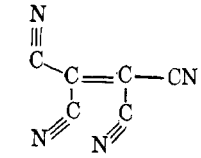
Neither Tubercidin nor Toyocamycin has been synthesized. Attempts to prepare Tubercidin were unsuccessful because of failure of the ribosidation step.[22] No attempts have been reported to prepare Toyocamycin, apparently because the only previously available synthetic routes to the pyrrolo[2,3-*d*]pyrimidine ring system, as discussed by Davoll[11] and commencing with pyrimidine intermediates, are not applicable to the preparation of the intermediate requisite for the introduction of the desired cyano group in the pyrrole ring.

In this paper we describe a simple synthesis of the pyrrolo[2,3-*d*]pyrimidine ring system, utilizing *pyrrole* intermediates, which has permitted the preparation of the aglycones of both Tubercidin and Toyocamycin, as well as a number of 5-substituted derivatives of the aglycone of Tubercidin.

Careful examination of the structure of the aglycone of Toyocamycin (**2b**) reveals a striking formal relationship to tetracyanoethylene (**3**). In fact, the latter



2b



3

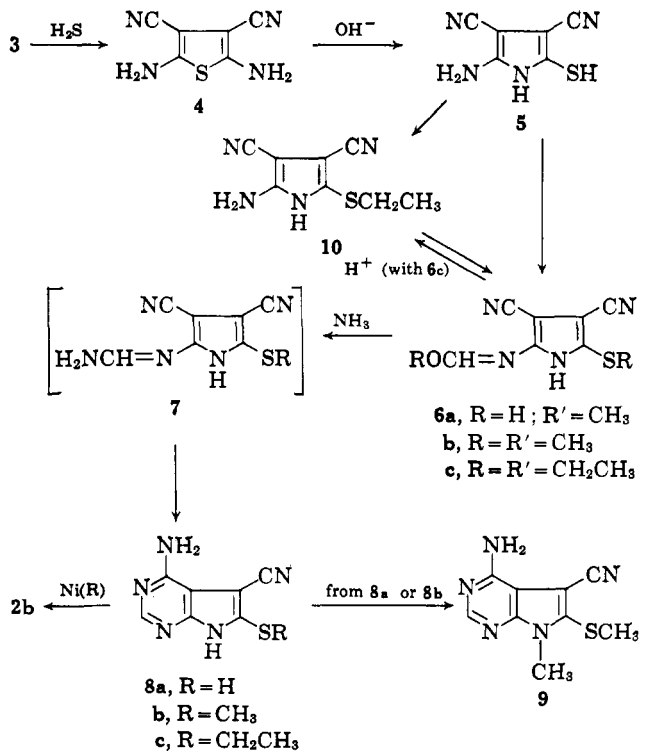
compound lacks but one carbon atom and one nitrogen atom of forming the entire Toyocamycin framework. We have been able to prepare the aglycone of Toyocamycin from tetracyanoethylene in five steps.

During their intensive investigation of the chemistry of tetracyanoethylene, Middleton and co-workers[23] reported its reaction with hydrogen sulfide to give 2,5-diamino-3,4-dicyanothiophene (**4**) and its subsequent base-catalyzed rearrangement to 2-mercapto-3,4-dicyano-5-aminopyrrole (**5**). It is immediately apparent that this latter pyrrole intermediate lacks but one carbon atom and one nitrogen atom of being the intact

(4) R. K. Robins, *J. Med. Chem.*, 7, 186 (1964).
(5) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides," Academic Press Inc., New York, N. Y., 1963, pp. 51–61.
(6) T. B. Johnson, *J. Am. Chem. Soc.*, **33**, 758 (1911).
(7) T. B. Johnson and E. F. Kohmann, *Am. Chem. J.*, **49**, 184 (1913).
(8) Z. Foldi, G. Fodor, I. Demjen, H. Szekeres, and I. Halmos, *Ber.*, **75**, 755 (1942).
(9) P. Nesbitt and P. Sykes, *J. Chem. Soc.*, 3057 (1954).
(10) Wellcome Foundation, Ltd., British Patent 812,366 (April 22, 1959); *Chem. Abstr.*, **54**, 592 (1960).
(11) J. Davoll, *J. Chem. Soc.*, 131 (1960).
(12) J. H. Bowie, A. W. Johnson, and G. Thomas, *Tetrahedron Letters*, No. **15**, 863 (1964).
(13) K. Anzai, G. Nakamura, and S. Suzuki, *J. Antibiotics* (Tokyo), **A10**, 201 (1957).
(14) S. Suzuki and S. Marumo, *ibid.*, **A13**, 360 (1960).
(15) S. Suzuki and S. Marumo, *ibid.*, **A14**, 34 (1961).
(16) Y. Mizuno, M. Ikehara, K. A. Watanabe, and S. Suzaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 1091 (1963).
(17) Y. Mizuno, M. Ikehara, K. A. Watanabe, S. Suzaki, and T. Itoh, *J. Org. Chem.*, **28**, 3329 (1963).
(18) G. Acs, E. Reich, and M. Mori, *Proc. Natl. Acad. Sci.*, **52**, 493 (1964).
(19) N. H. Nishimura, K. Katagiri, K. Sato, M. Mayama, and N. Shimaoka, *J. Antibiotics* (Tokyo), **A9**, 60 (1956).
(20) K. Ohkuma, *ibid.*, **A14**, 343 (1961).
(21) K. Ohkuma, *ibid.*, **A13**, 361 (1960).
(22) Y. Mizuno, M. Ikehara, K. A. Watanabe, and S. Suzaki, *J. Org. Chem.*, **28**, 3331 (1963).
(23) W. J. Middleton, V. A. Engelhardt, and B. S. Fisher, *J. Am. Chem. Soc.*, **80**, 2822 (1958).

Toyocamycin skeleton. Previous investigations in this laboratory on the conversion of *o*-aminonitriles to fused 4-aminopyrimidine heterocycles[24] would lead one to anticipate with confidence the conversion of **5** to a 6-mercapto derivative of the Toyocamycin aglycone, which should be capable of conversion to **2b** by desulfurization.

2-Mercapto-3,4-dicyano-5-aminopyrrole (**5**) was treated with trimethyl orthoformate to give what was expected to be the intermediate methoxymethylenamino derivative **6a** which was not isolated but treated directly with ammonia. Previous studies[24] have shown that this sequence of reactions results in the intermediate formation of a formamidine (such as **7**) which cyclizes under the basic reaction conditions to a fused 4-aminopyrimidine. It was thus anticipated that the product of this sequence of reactions would be the 6-mercapto derivative **8a** of the aglycone of Toyocamycin. Microanalysis of the product indicated, however, the presence of one additional CH_2 group. N.m.r. analysis confirmed the presence of a methyl group (singlet at 2.43 p.p.m., integration three protons, in trifluoroacetic acid as solvent); the lack of solubility of this product in dilute sodium bicarbonate suggested that the compound no longer contained a free mercapto group. The product thus appeared to be the 6-methylmercapto derivative **8b**; this structural assignment was confirmed by Raney nickel desulfurization[25] to give 4-amino-5-cyanopyrrolo[2,3-*d*]pyrimidine (**2b**), the aglycone of Toyocamycin. The ultraviolet spectrum of **2b** is almost identical in shape and position of maxima with that reported for Toyocamycin itself.[19,20] Its infrared spectrum exhibits a nitrile band at 2220 cm.$^{-1}$; the corresponding absorption band in Toyocamycin is reported to occur at 2230 cm.$^{-1}$.[20]



(24) E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).

(25) D. J. Brown, *J. Soc. Chem. Ind.* (London), **69**, 353 (1950).

An alternative synthetic route to the desired aglycone of Toyocamycin (**2b**) involved the direct annulation of the fused 4-aminopyrimidine ring to the *o*-aminonitrile **5** by the use of formamidine acetate, a reagent which has been used previously in these laboratories for analogous conversions.[26] The reaction of **5** with formamidine acetate in 2-ethoxyethanol was, however, accompanied by considerable decomposition. Attempted recrystallization of the dark brown reaction product did not result in significant purification. The crude product **8a** was therefore directly desulfurized with Raney nickel to give the desired aglycone **2b** as a white microcrystalline solid which did not melt below 360°, identical in every respect with the product obtained by desulfurization of the 6-methylmercapto derivative **8b**, as described above.

Although 4-amino-5-cyano-6-mercaptopyrrolo-[2,3-*d*]pyrimidine (**8a**) could not be isolated in pure form from the above reaction, it was characterized as its dimethyl derivative (presumably the 6,7 isomer) **9** by methylation with methyl iodide in dilute sodium hydroxide. This dimethyl derivative was identical with the product obtained by treatment of 4-amino-5-cyano-6-methylmercaptopyrrolo[2,3-*d*]pyrimidine (**8b**) under similar conditions.

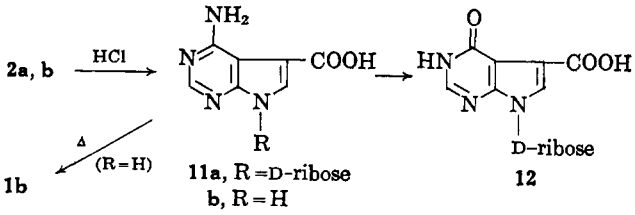
Treatment of 2-mercapto-3,4-dicyano-5-aminopyrrole (**5**) with triethyl orthoformate, followed by reaction with alcoholic ammonia, gave 4-amino-5-cyano-6-ethylmercaptopyrrolo[2,3-*d*]pyrimidine (**8c**). The presence of an ethyl group in the product was confirmed both by elemental analysis and by examination of its n.m.r. spectrum, which exhibited a triplet centered at 1.0 and a quadruplet centered at 2.85 p.p.m. (in trifluoroacetic acid as solvent). Despite the fact that attempts to desulfurize **8c** were inexplicably unsuccessful, the ethyl group is believed to be on sulfur, both by analogy with the known structure of **8b** and because of the extremely close similarity of the ultraviolet and infrared spectra of **8b** and **8c**. That alkylation by the orthoformate esters took place prior to treatment of the reaction mixture with ammonia was shown by the following sequence of interconversions. The intermediate ethoxymethylenamino derivative **6c**, prepared from **5** with triethyl orthoformate, was hydrolyzed by dilute hydrochloric acid to give 2-amino-3,4-dicyano-5-ethylmercaptopyrrole (**10**), which was synthesized independently from **5** by reaction with ethyl iodide in the presence of sodium bicarbonate. Treatment of **10** with triethyl orthoformate regenerated **6c**.

To our knowledge the only previously reported alkylation on sulfur by an orthoformate ester involved the conversion of 2-mercapto-4-aminopyrimidine-5-carboxamide to 2-ethylmercapto-5(6H)pyrimido[4,5-*d*]-pyrimidone with a mixture of triethyl orthoformate and acetic anhydride.[27a] Alkylations of this type on nitrogen have been observed by Roberts and Vogt,[27b] who reported that aniline was converted to N-phenyl-N-ethylformamide upon treatment with triethyl orthoformate. We make particular note of this unusual sulfur alkylation reaction because of the wide-spread use of orthoformate esters.

(26) E. C. Taylor and W. A. Ehrhart, *J. Am. Chem. Soc.*, **82**, 3138 (1960).

(27) (a) S. K. Chatterjee and N. Anand, *J. Sci. Ind. Res.* (India), **17B**, 63 (1958); (b) R. M. Roberts and P. J. Vogt, *J. Am. Chem. Soc.*, **78**, 4778 (1956).

Okhuma has shown in his original degradative work on Toyocamycin[20] that hydrolysis of the nitrile grouping with hydrochloric acid gave the carboxylic acid **11a** which upon treatment with nitrous acid gave **12**. We have been able to show that **2b**, the aglycone of Toyocamycin, can be hydrolyzed under similar conditions to give the corresponding 5-carboxylic acid **11b**,



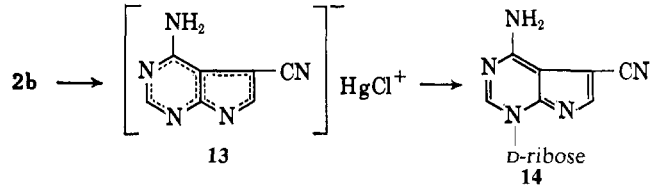
which was successfully decarboxylated by heating in quinoline in the presence of its copper salt.[28] The product of decarboxylation was 4-aminopyrrolo[2,3-*d*]-pyrimidine (**1b**), the aglycone of Tubercidin. This latter sequence not only confirms the structure assigned to **2b** but provides an alternative synthetic route to **1b** commencing with a pyrrole rather than a pyrimidine intermediate.

Attempts to convert 4-amino-5-cyanopyrrolo[2,3-*d*]-pyrimidine (**2b**) into Toyocamycin itself by ribosidation have unfortunately been unsuccessful. The problem of preparing nucleosides from purines and related heterocyclic bases has received intensive study since the report by Fischer and Helferich[29] that the silver salt of the purine could be condensed in hot xylene solution with a poly-O-acylglycosyl halide to give an O-acylated nucleoside, which could then be deacylated. The later demonstration by Davoll and Lowy[30] that the monochloromercury derivatives of certain purines could be employed to greater advantage than the corresponding silver derivatives for the preparation of purine nucleosides has found widespread acceptance and use. Although the silver and chloromercury procedures can be applied only with difficulty to purines containing an amino group basic enough to react with the glycosyl halide, it has been found possible to effect reaction in much better yield if the amino group is acetylated prior to reaction of the compound with the glycosyl halide.[5,30,31]

Our first attempts to prepare the nucleoside of **2b** involved, therefore, its initial treatment with acetic anhydride in the presence of pyridine in the hopes of obtaining a monoacetyl derivative which could then be converted to a metal salt and subsequently ribosidated. The product of acetylation, however, appeared to be a diacetyl derivative which was intractable. A similar difficulty was experienced by other workers[22] in an attempt to prepare a 4-acylaminopyrrolo[2,3-*d*]pyrimidine; the N-4(7)-diacetyl and -dibenzoyl derivatives were obtained, and specific removal of the N-7-acyl group was found to be impossible. We therefore omitted the acetylation step and treated **2b** directly with mercuric chloride in aqueous sodium hydroxide solution to give the chloromercury derivative **13** directly in 82% yield. Condensation of **13** with 1-chloro-2,3,5-tri-O-acetyl-β-D-ribofuranose in boiling toluene gave a light brown sirup which was deacetylated with alcoholic ammonia. Fractional crystallization of this crude material gave a small amount of a nucleoside which melted at 244–245.5° (Kofler block), whose infrared spectrum was essentially superimposable upon that of Toyocamycin.[32] Its ultraviolet spectra ($\lambda_{max}^{0.1\ N NaOH}$ 229 mμ (ε 13,700) and 277 mμ (ε 17,200), $\lambda_{max}^{0.1\ N HCl}$ 234 mμ (ε 18,700) and 274 mμ (ε 14,400)), are almost identical with those reported for Toyocamycin ($\lambda_{max}^{0.1\ N NaOH}$ 232 mμ (ε 10,000) and 279 mμ (ε 14,800), $\lambda_{max}^{0.1\ N HCl}$ 234 mμ (ε 18,200) and 274 mμ (ε 13,200)).[20] However, paper chromatographic comparison of our synthetic riboside with authentic Toyocamycin (Table I) definitely established their nonidentity. We believe on the basis of the ultraviolet and infrared spectra of our synthetic nucleoside, and on the basis of its chromatographic behavior, that we have in hand the 1-ribosyl derivative **14** rather than the 7-ribosyl derivative **2a**.

Table I. Paper Chromatographic Comparison of Toyocamycin (**2a**) with 1-(D-ribosyl)-4-amino-5-cyanopyrrolo[2,3-*d*]-pyrimidine (**14**)

Solvent system	R_f values: Toyocamycin	R_f values: Compd. **14**
1% ammonium hydroxide–1-propanol (1:2)	0.70	0.70
4% aqueous ammonium chloride	0.51	0.52
Water–acetone (1:1)	0.75	0.75
Methanol–water–1-butanol (1:2:4)	0.65	0.62 (major) 0.72 (trace)
1-Butanol saturated with water at 20°	0.53	0.51 (major) 0.67 (trace)

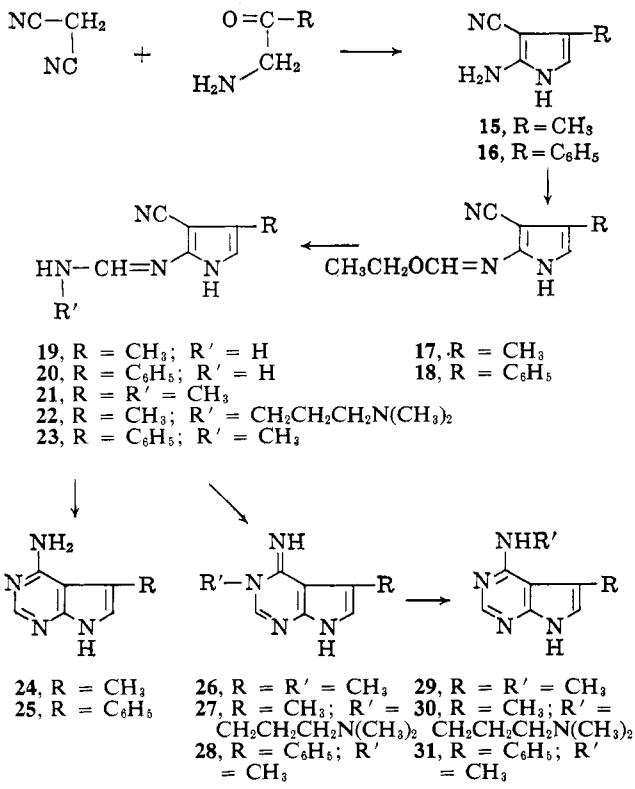


Efforts are currently being made to circumvent the above difficulties encountered in direct ribosidation of the intact aglycone, by introducing the ribosyl grouping into a pyrrole precursor, with annulation of the pyrimidine ring as the terminal synthetic step. This route should obviate difficulties involving participation of the pyrimidine ring nitrogens, as well as the 4-amino group, in the ribosidation reaction, and should provide as well a useful intermediate for the preparation of structural analogs of Toyocamycin which differ from the natural antibiotic in modifications in the pyrimidine ring rather than in the pyrrole ring.

We wish to describe at the present time another, but closely related, synthesis of pyrrolo[2,3-*d*]pyrimidines *via* pyrrole intermediates which has provided structural analogs of the aglycones of Toyocamycin and Tubercidin differing from the latter by substitution in the pyrrole ring. This synthetic approach was inspired by a recent report by Gewald[33] that α-amino ketones

(28) E. Piers and R. K. Brown, *Can. J. Chem.*, **40**, 559 (1962).
(29) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914).
(30) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **73**, 1650 (1951).
(31) J. J. Fox and I. Wempen in "Advances in Carbohydrate Chemistry," Vol. 14, M. L. Wolfrom and R. S. Tipson, Ed., Academic Press Inc., New York, N. Y., 1959, pp. 283–310.
(32) We are indebted to Dr. Saburo Suzuki of the Institute of Physical and Chemical Research, Tokyo, for a small sample of authentic Toyocamycin.
(33) K. Gewald, *Z. Chem.*, **1**, 349 (1961).

such as aminoacetone and ω-aminoacetophenone condense with malononitrile to give 2-amino-3-cyano-4-methylpyrrole (**15**) and 2-amino-3-cyano-4-phenylpyrrole (**16**), respectively. Treatment of the intermediates **15** and **16** with triethyl orthoformate, followed by removal of excess reagent by distillation and treatment of the resulting ethoxymethylenamino derivatives (**17** and **18**) with ammonia, gave the amidines **19** and **20**. That cyclization to pyrrolo[2,3-*d*]pyrimidines had not occurred was clearly indicated by the presence of a nitrile band at 2200 cm.$^{-1}$ in the infrared spectra of the products. Treatment of these intermediate amidines with sodium methoxide in pyridine resulted in cyclization to the desired pyrrolo[2,3-*d*]pyrimidines **24** and **25**. The fact that cyclization of the intermediate formamidines across the *ortho*-situated nitriles had not occurred in alcoholic ammonia, in contrast to the previously discussed synthesis of the aglycone of Toyocamycin (**2b**) in which intramolecular cyclization had occurred under analogous conditions, emphasizes the effect of the second nitrile group in the pyrrole ring in increasing



15, R = CH_3
16, R = C_6H_5

19, R = CH_3; R′ = H
20, R = C_6H_5; R′ = H
21, R = R′ = CH_3
22, R = CH_3; R′ = $CH_2CH_2CH_2N(CH_3)_2$
23, R = C_6H_5; R′ = CH_3

17, R = CH_3
18, R = C_6H_5

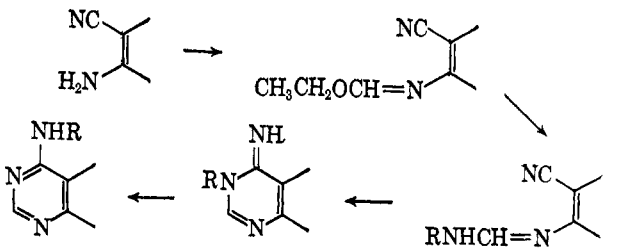
24, R = CH_3
25, R = C_6H_5

26, R = R′ = CH_3
27, R = CH_3; R′ = $CH_2CH_2CH_2N(CH_3)_2$
28, R = C_6H_5; R′ = CH_3

29, R = R′ = CH_3
30, R = CH_3; R′ = $CH_2CH_2CH_2N(CH_3)_2$
31, R = C_6H_5; R′ = CH_3

the electrophilic character of the nitrile grouping participating in the cyclization.

Previous work in these laboratories concerned with the preparation of fused 4-amino- and 4-substituted aminopyrimidines from *o*-aminonitriles *via* *o*-ethoxymethylenaminonitriles[24] has indicated that the reaction course proceeds stepwise *via* the intermediate steps indicated in the reaction scheme below. We have been able to demonstrate that an analogous sequence of reactions is encountered with the pyrrole intermediates **15** and **16**. Thus, treatment of **15** with triethyl orthoformate followed by direct reaction of the resulting ethoxymethylenaminopyrrole **17** with methylamine in ethanolic solution gave (*via* the intermediate formamidine **21**) the pyrrolo[2,3-*d*]pyrimidine (**26**). It is of interest to note that cyclization of the formamidine **21**



takes place in the presence of methylamine, although no cyclization takes place with the desmethyl analog **19**. Although **26** was stable to sodium methoxide in refluxing ethanol, it rearranged smoothly in boiling water to the isomeric exocyclic methylamino derivative **29**. Similarly, the ethoxymethylenamino intermediate **17** on reaction with 3-dimethylaminopropylamine in refluxing ethanol gave (*via* **22**) the initial cyclization product **27** which rearranged analogously in boiling water to its aromatic isomer **30**. The fact that rearrangement of **26** and **27** to **29** and **30**, respectively, took place with boiling water and not with sodium methoxide indicates the hydrolytic nature of the ring-opening reaction which is a necessary prelude to rearrangement.

In analogous fashion, 2-amino-3-cyano-4-phenylpyrrole (**16**) was converted with triethyl orthoformate followed by condensation with methylamine to the pyrrolo[2,3-*d*]pyrimidine **28** which was rearranged to 4-methylamino-5-phenylpyrrolo[2,3-*d*]pyrimidine (**31**) by heating in aqueous ethanol.

In view of the difficulties encountered in the introduction of a ribosyl grouping into the correct (7) position on the pyrrole ring of the aglycone of Toyocamycin, no attempts have been made to ribosidate these 5-substituted derivatives of 4-aminopyrrolo[2,3-*d*]-pyrimidine. Instead, our current efforts at the preparation of structural analogs of Toyocamycin and Tubercidin are concerned with the introduction of the ribosyl grouping into pyrrole intermediates such as **5** and **10**, which will then be cyclized to the intact nucleosides. The results of these synthetic approaches to pyrrolo-[2,3-*d*]pyrimidine nucleosides *via* pyrrole nucleosides will be reported independently.

Ultraviolet data are given in Table II.

Experimental[34]

4-Amino-5-cyano-6-methylmercaptopyrrolo[2,3-d]-pyrimidine (**8b**). A solution of 1 g. of 2-amino-3,4-dicyano-5-mercaptopyrrole[23] in 25 ml. of trimethyl orthoformate was heated under reflux for 5 hr. and then evaporated to dryness under reduced pressure. The tan residue was covered with 20 ml. of ethanolic ammonia (saturated at 0°) and allowed to stand for 2 days at room temperature. Evaporation to dryness then gave 1.1 g. of crude product which was purified by sublimation at 230° (0.05 mm.) to give 0.42 g. (34%) of a light tan solid, m.p. 310° dec. The analytical sample, m.p. 317–318° dec., was prepared by recrystallization from methanol

Anal. Calcd. for $C_8H_7N_5S$: C, 46.83; H, 3.44; N, 34.12; S, 15.60. Found: C, 46.76; H, 3.61; N, 33.99; S, 15.50.

(34) All melting points were determined on a Thomas–Hoover silicone bath apparatus and are uncorrected. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich., and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Table II. Ultraviolet Spectra

Compd.	Solvent	λ_{max}, mμ	$\epsilon \times 10^{-3}$
4-Amino-5-cyano-6-methylmercaptopyrrolo[2,3-*d*]pyrimidine (**8b**)	*a*	231, 301	16.5, 17.6
4-Amino-5-cyano-6-mercaptopyrrolo[2,3-*d*]pyrimidine (**8a**)	*d*	241, 327	
4-Amino-5-cyanopyrrolo[2,3-*d*]pyrimidine (**2b**)	*a*	226, 277, 287	10.7, 13.7, 9.6
	b	245, 289	14.4, 10.0
	c	239, 274	13.6, 11.5
4-Amino-5-cyano-6-methylmercapto-7-methylpyrrolo-[2,3-*d*]pyrimidine (**9**)	*a*	235, 269, 327	17.4, 12.2, 13.9
4-Amino-5-cyano-6-ethylmercaptopyrrolo[2,3-*d*]pyrimidine (**8c**)	*a*	229 (sh), 301	15.7, 17.5
3,4-Dicyano-2-ethoxymethylenamino-5-ethylmercapto-pyrrole (**6c**)	*a*	282	14.1
2-Amino-3,4-dicyano-5-ethylmercaptopyrrole (**10**)	*a*	224, 256, 300	14.4, 6.2, 10.5
4-Aminopyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid (**11b**)	*b*	226, 259, 280	10.3, 9.5, 11.0
	c	228, 240 (sh), 274	10.4, 9.1, 11.1
4-Aminopyrrolo[2,3-*d*]pyrimidine (**1b**)	*b*	272	10.4
	c	224, 274	17.5, 10.3
1-(D-Ribosyl)-4-amino-5-cyanopyrrolo[2,3-*d*]pyrimidine (**14**)	*b*	229, 277	13.7, 17.2
	c	234, 274	18.7, 14.4
Toyocamycin (**2a**)[e]	*b*	232, 279	10.0, 14.8
	c	234, 274	18.2, 13.2
	d	230, 279	10.5, 16.1
3-Cyano-2-formamidino-4-methylpyrrole (**19**)	*d*	295	
3-Cyano-2-formamidino-4-phenylpyrrole (**20**)	*a*	229, 305	19.1, 12.9
	c	275	10.0
4-Amino-5-methylpyrrolo[2,3-*d*]pyrimidine (**24**)	*a*	279	8.7
	b	278	8.0
	c	231, 284	21.0, 8.6
4-Amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (**25**)	*a*	230, 255, 282	10.4, 10.1, 13.4
	b	239, 283	11.4, 11.3
	c	240, 286	14.6, 10.9
3,5-Dimethyl-4(3H)-iminopyrrolo[2,3-*d*]pyrimidine (**26**)	*a*	231, 273	12.8, 8.1
	b	271	9.7
	c	231, 286	20.3, 8.0
4-Methylamino-5-methylpyrrolo[2,3-*d*]pyrimidine (**29**)	*a*	282	10.3
	b	281	10.3
	c	234, 282	16.9, 10.5
3-(3-Dimethylaminopropyl)-4(3H)-imino-5-methylpyrrolo-[2,3-*d*]pyrimidine (**27**)	*a*	230, 274	12.3, 9.3
	b	273	9.6
	c	234, 288	21.2, 8.2
4-(3-Dimethylaminopropyl)amino-5-methylpyrrolo-[2,3-*d*]pyrimidine (**30**)	*a*	283	11.3
	b	281	10.9
	c	237, 285	15.8, 9.5
3-Methyl-4(3H)-imino-5-phenylpyrrolo[2,3-*d*]pyrimidine (**28**)	*a*	243–253, 282	10.3, 12.5
	b	273	12.2
	c	240, 288	14.0, 10.7
4-Methylamino-5-phenylpyrrolo[2,3-*d*]pyrimidine (**31**)	*a*	262 (sh), 283	11.2, 15.4
	b	282	14.1
	c	250, 285	13.4, 12.8

[a] Ethanol. [b] 0.1 *N* NaOH. [c] 0.1 *N* HCl. [d] Methanol. [e] Values estimated from the spectra of Toyocamycin as published by Ohkuma.[20]

4-Amino-5-cyano-6-mercaptopyrrolo[2,3-d]pyrimidine (**8a**). To a solution of 1.64 g. of 2-amino-3,4-dicyano-5-mercaptopyrrole[23] in 40 ml. of 2-ethoxyethanol was added 2.08 g. (2 equiv.) of formamidine acetate[26] and the mixture was heated under reflux for 1 hr. Evolution of ammonia commenced immediately. After 1 hr. the solution was cooled and evaporated to dryness under reduced pressure. The residue was triturated with water and filtered to give 1.6 g. of crude product which did not melt below 360°. Attempted crystallization was unsuccessful, and the compound was therefore characterized as its dimethyl derivative **9**, *vide infra*.

4-Amino-5-cyanopyrrolo[2,3-d]pyrimidine (**2b**). *Method A.* To a slurry of 0.5 g. of 4-amino-5-cyano-6-methylmercaptopyrrolo[2,3-*d*]pyrimidine (**8b**) in 10 ml. of water containing 1 ml. of concentrated ammonium hydroxide was added *ca.* 1.5 g. (0.5 teaspoon) of freshly prepared Raney nickel[25] and the mixture was heated under reflux for 18 hr. It was filtered hot and the nickel was extracted several times with boiling water. Concentration of the combined filtrate and extracts gave on cooling 0.14 g. of product, contaminated with a small amount of unreacted starting material. Recrystallization from butanol, then aqueous dimethylformamide, and finally dimethylformamide gave the analytical sample, m.p. >360°.

Anal. Calcd. for $C_7H_5N_5$: C, 52.82; H, 3.17; N, 44.01. Found: C, 52.79; H, 3.24; N, 43.49.

Method B. To a solution of 2.36 g. of crude 4-amino-5-cyano-6-mercaptopyrrolo[2,3-*d*]pyrimidine in 50 ml. of water containing 5 ml. of concentrated ammonium hydroxide was added *ca.* 8 g. (2.5 teaspoons) of freshly prepared Raney nickel.[25] The mixture was heated under reflux for 18 hr., filtered hot, and the filtrate was cooled to give 0.3 g. of crude product. An additional 0.4 g. was obtained by Soxhlet extraction of the

nickel with hot water. The combined crude product was extracted with 5% sodium bicarbonate (to remove traces of unreacted starting material) and recrystallized from dimethylformamide to give 0.51 g. (26%), m.p. >360°, identical with the material prepared by method A.

4-Amino-5-cyano-6-methylmercapto-7-methylpyrrolo[2,3-d]pyrimidine (**9**). *Method A.* A mixture of 0.6 g. of crude 4-amino-5-cyano-6-mercaptopyrrolo[2,3-*d*]pyrimidine, 10 ml. of methyl iodide, and 20 ml. of 5% sodium hydroxide solution was heated at 50° for 6 hr. (with a reflux condenser attached), with occasional shaking. The cooled reaction mixture was evaporated under reduced pressure to remove excess methyl iodide; filtration then gave a dark brown solid which was washed with water and purified by sublimation at 250° (0.5 mm.). Recrystallization of the sublimate from ethanol gave colorless crystals, m.p. 315–317° dec.

Anal. Calcd. for $C_9H_9N_5S$: C, 49.31; H, 4.14; N, 31.95. Found: C, 49.24; H, 4.51; N, 31.59.

Method B. Methylation of 0.3 g. of 4-amino-5-cyano-6-methylmercaptopyrrolo[2,3-*d*]pyrimidine under analogous conditions gave 0.2 g. (63%) of colorless crystals, identical with the material prepared by method A.

4-Amino-5-cyano-6-ethylmercaptopyrrolo[2,3-d]pyrimidine (**8c**). A mixture of 7 g. of 2-amino-3,4-dicyano-5-mercaptopyrrole and 100 ml. of triethyl orthoformate was heated under reflux for 6 hr. and then evaporated to a sirup under reduced pressure. The residue was dissolved in 100 ml. of ethanol and 50 ml. of ethanolic ammonia (saturated at 0°) was added. The solution was allowed to stand at room temperature for 2 days and was then evaporated to dryness under reduced pressure to give 9.3 g. of crude product. Sublimation at 210° (0.5 mm.) gave 6.4 g. (78%) of a light tan powder, m.p. 310° dec. Recrystallization from ethanol then gave white crystals, m.p. 316–317° dec.

Anal. Calcd. for $C_9H_9N_5S$: C, 49.31; H, 4.14; N, 31.95; S, 14.60. Found: C, 49.40; H, 4.31; N, 31.83; S, 14.86.

2-Ethoxymethylenamino-3,4-dicyano-5-ethylmercaptopyrrole (**6c**). A mixture of 2.0 g. of 2-amino-3,4-dicyano-5-mercaptopyrrole and 40 ml. of triethyl orthoformate was heated under reflux for 5 hr. and then evaporated under reduced pressure to a sirup which solidified on standing. The solid residue was extracted several times with a total of 800 ml. of boiling carbon tetrachloride, the extracts were combined and evaporated to dryness, and the residue was recrystallized from carbon tetrachloride (charcoal) to give 2.5 g. (83%) of white needles, m.p. 127–129°.

Anal. Calcd. for $C_{11}H_{12}N_4OS$: C, 53.22; H, 4.87; N, 22.57; S, 12.90. Found: C, 52.86; H, 4.96; N, 22.62; S, 12.95.

2-Amino-3,4-dicyano-5-ethylmercaptopyrrole (**10**). *Method A.* A solution of 2.0 g. of 2-amino-3,4-dicyano-5-mercaptopyrrole in 20 ml. of 5% sodium bicarbonate solution was treated with 10 ml. of ethyl iodide and the mixture shaken for 15 min. An additional 10 ml. of ethyl iodide and 10 ml. of 5% sodium bicarbonate solution were added and the solution was shaken for 1 hr. The mixture was chilled to 0° and filtered to give 1.7 g. (73%) of a tan solid, m.p. 177–179°. The analytical sample was obtained as white needles, m.p. 184–186°, by recrystallization from water followed by vacuum sublimation.

Anal. Calcd. for $C_8H_8N_4S$: C, 49.99; H, 4.20; N, 29.16; S, 16.65. Found: C, 50.21; H, 4.43; N, 29.10; S, 16.69.

Method B. A solution of 1.0 g. of 2-ethoxymethylenamino-3,4-dicyano-5-ethylmercaptopyrrole in 25 ml. of 10% hydrochloric acid was heated under reflux for 15 min., cooled, and neutralized with 10% sodium hydroxide. The solid which precipitated was collected by filtration, m.p. 173–175°. It was identical with the material prepared by method A.

4-Aminopyrrolo[2,3-d]pyrimidine-5-carboxylic Acid (**11b**). A solution of 0.5 g. of 4-amino-5-cyanopyrrolo[2,3-*d*]pyrimidine in 20 ml. of 6 *N* hydrochloric acid was heated under reflux, under nitrogen, for 4 hr. Cooling and filtering gave 0.4 g. (59%) of the hydrochloride salt of the 5-carboxylic acid. Recrystallization from 2 *N* hydrochloric acid (charcoal) gave the analytical sample, m.p. 286–287° dec.

Anal. Calcd. for $C_7H_6N_4O_2 \cdot HCl$: C, 39.01; H, 3.26; N, 26.10. Found: C, 39.06; H, 3.56; N, 26.26.

4-Aminopyrrolo[2,3-d]pyrimidine (**1b**). A mixture of 0.2 g. of 4-aminopyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid (prepared from the hydrochloride by addition of dilute ammonium hydroxide to a hot solution of the salt in water) and *ca.* 0.01 g. of its copper salt (prepared by dissolution of the acid in 1 equiv. of hot sodium bicarbonate solution, followed by addition of 1 equiv. of cupric sulfate) was heated in 2 ml. of quinoline at 210° for 2 hr. The solution was then evaporated to dryness under reduced pressure and the residue was sublimed at 150° (0.05 mm.) to give 38 mg. (33% after correction for recovered starting material). Recrystallization from water (charcoal) gave white needles, m.p. 254–255° dec. (lit. m.p. 252–254°,[11] 255–257°[15]). Its infrared spectrum was identical with the spectrum of 4-aminopyrrolo[2,3-*d*]pyrimidine.[15]

Chloromercury Derivative of 4-amino-5-cyanopyrrolo[2,3-d]pyrimidine (**13**). To a solution of 0.8 g. of 4-amino-5-cyanopyrrolo[2,3-*d*]pyrimidine in 75 ml. of water containing 1.05 ml. of 6 *N* sodium hydroxide (1 equiv.) was added 1.71 g. (1 equiv.) of mercuric chloride dissolved in 50 ml. of ethanol. An immediate precipitate of the chloromercury derivative resulted. The mixture was stirred for 10 min. and centrifuged, and the collected solid was washed with water, dimethylformamide, water, and finally ethanol (with centrifugation rather than filtration). The product was dried over phosphorus pentoxide to give 1.61 g. (82%) of a light yellow powder.

1-(D-Ribosyl)-4-amino-5-cyanopyrrolo[2,3-d]pyrimidine (**14**). A suspension of 0.8 g. of the finely powdered, dried (over phosphorus pentoxide) chloromercury derivative of 4-amino-5-cyanopyrrolo[2,3-*d*]pyrimidine in 100 ml. of reagent grade toluene was added to a three-necked, 100-ml. flask fitted with an addition funnel, a take-off distillation head, and a Hershberg wire stirrer. The system was protected from moisture by means of a silica gel drying tube, and *ca.* 50 ml. of toluene was removed by distillation to ensure an

anhydrous solution. A toluene solution of freshly prepared 1-chloro-2,3,5-tri-O-acetyl-β-D-ribofuranose (from 1.6 g. of the tetraacetate)[35] was added in one portion to the hot toluene suspension *via* the addition funnel, and the solution was stirred vigorously and heated under reflux for 1 hr. During this period a small amount of toluene was continuously removed by distillation to ensure anhydrous reaction conditions.

The reaction mixture was then cooled and concentrated to *ca.* 10 ml. under reduced pressure, and the residue was triturated with 60 ml. of petroleum ether (b.p. 60–70°) and filtered. The tan solid was extracted with three 20-ml. portions of hot chloroform and the extracts were washed with 30% aqueous potassium iodide and then with water. The chloroform solutions were combined, dried over anhydrous sodium sulfate, and evaporated to dryness, the residual sirup was dissolved in 30 ml. of methanol, and the solution was saturated with ammonia at 0°. After standing overnight, the methanolic solution was evaporated to give a sirup which was dissolved in hot ethanol; cooling resulted in the separation of 7 mg. of a fine white powder.

The ethanol filtrate was concentrated to *ca.* 10 ml., 4 g. of acid-washed alumina was added, and the solvent was allowed to evaporate at 50°. The alumina (carrying the absorbed product) was slurried in ethyl acetate and added to the top of a previously prepared column of acid-washed alumina contained in a 50-ml. buret and covered with ethyl acetate. The column was washed with 200 ml. of ethyl acetate and the washings were discarded. Elution of the column with methanol–ethyl acetate (1:3), collection of the eluates which absorbed in the ultraviolet at 278 mμ, and evaporation of the eluates to dryness under reduced pressure gave an additional 4 mg. of a white powder, identical in infrared spectrum with the 7 mg. of product obtained above.

The combined solids were extracted with 1 ml. of boiling water and the insoluble material (3 mg.) was examined and then discarded. Cooling of the filtrate yielded 6 mg. of white microcrystals, m.p. 244–245.5°. Toyocamycin itself melts at 239–242° under the same conditions (lit.[19] m.p. 243°).

Anal. Calcd. for $C_{12}H_{13}N_5O_4$: C, 49.53; H, 4.50; N, 24.07. Found: C, 50.00; H, 4.46; N, 27.10.[36]

2-Formamidino-3-cyano-4-methylpyrrole (**19**). A suspension of 2.0 g. of 2-amino-3-cyano-4-methylpyrrole[33] in 25 ml. of triethyl orthoformate was heated under reflux for 2 hr. and then evaporated to dryness under reduced pressure. The residue was covered with 25 ml. of ethanolic ammonia (saturated at 0°) and allowed to stand for 2 days at room temperature. Evaporation of the reaction mixture to dryness under reduced pressure gave 1.5 g. (61%) of a red-brown solid, m.p. 163° dec. The infrared spectrum of this material exhibited a nitrile band at 2200 cm.$^{-1}$. It proved to be too unstable for recrystallization and was used directly in the cyclization step described below.

4-Amino-5-methylpyrrolo[2,3-d]pyrimidine (**24**). A mixture of 3.0 g. of crude 2-formamidino-3-cyano-4-methylpyrrole in 50 ml. of ethanol containing 1.0 g. of sodium methoxide was heated under reflux for 1 hr., and the reaction mixture was then evaporated to dryness under reduced pressure. Sublimation of the residue at 170° (0.05 mm.) gave 2.72 g. (91%) of a colorless solid, m.p. 256–258° dec. The product was obtained in the form of long, colorless needles, m.p. 257–258° dec. upon recrystallization from acetonitrile.

Anal. Calcd. for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.82. Found: C, 56.78; H, 5.42; N, 37.78.

2-Formamidino-3-cyano-4-phenylpyrrole (**20**). A mixture of 1.0 g. of 2-amino-3-cyano-4-phenylpyrrole[33] and 20 ml. of triethyl orthoformate was heated under reflux for 1 hr., evaporated to dryness, and treated with ethanolic ammonia as described above for the corresponding 4-methyl analog **19** to give 0.43 g. (38%) of product. Recrystallization from ethanol gave white platelets, m.p. 240° dec.

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.51; H, 4.79; N, 26.76.

4-Amino-5-phenylpyrrolo[2,3-d]pyrimidine (**25**). A solution of 8.0 g. of 2-formamidino-3-cyano-4-phenylpyrrole in 400 ml. of ethanol containing 3 g. of sodium methoxide was heated under reflux for 1 hr. and evaporated to dryness under reduced pressure, and the residue was digested with cold water and filtered to give 7.4 g. (93%) of product. Recrystallization from ethanol gave colorless crystals, m.p. 259–251° dec.

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.48; H, 4.88; N, 26.60.

3,5-Dimethyl-4(3H)-iminopyrrolo[2,3-d]pyrimidine (**26**). A suspension of 1.0 g. of 2-amino-3-cyano-4-methylpyrrole in 25 ml. of triethyl orthoformate was heated under reflux for 2 hr., cooled, and evaporated to near dryness under reduced pressure. The residue was dissolved in 25 ml. of ethanolic methylamine (saturated at 0°) and allowed to stand at room temperature for 2 days. Evaporation of the solution to dryness gave a tan solid which was sublimed at 180° (0.05 mm.) to give a light tan solid, m.p. 245–250° dec. Recrystallization from acetonitrile (charcoal) gave 0.53 g. (39%) of white needles, m.p. 250–251.5° dec.

Anal. Calcd. for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.55. Found: C, 59.52; H, 6.07; N, 34.45.

4-Methylamino-5-methylpyrrolo[2,3-d]pyrimidine (**29**). A solution of 0.1 g. of 3,5-dimethyl-4(3*H*)-iminopyrrolo[2,3-*d*]pyrimidine in 7 ml. of water was heated under reflux for 1 hr., cooled, and filtered to give 0.08 g. (80%) of white crystals. Recrystallization from water then gave fine white needles, m.p. 237.5–239° dec.

Anal. Calcd. for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.55. Found: C, 59.27; H, 5.95; N, 34.69.

3-(3-Dimethylaminopropyl)-4(3H)-imino-5-methylpyrrolo[2,3-d]pyrimidine (**27**). A suspension of 2.0 g. of 2-amino-3-cyano-4-methylpyrrole in 50 ml. of triethyl orthoformate was heated under reflux for 2 hr., cooled, and evaporated to dryness under reduced pressure. The residue was dissolved in 20 ml. of ethanol, 5 ml. of 3-dimethylaminopropylamine was added, and the mixture was heated under reflux for 7 hr. and evaporated under reduced pressure. The residual sirup was dissolved in 20 ml. of ethanol and then diluted with 500 ml. of petroleum ether (b.p. 60–70°). Cooling resulted in the separation of 0.83 g.

(35) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

(36) The microanalyses were carried out on extremely small samples; the high nitrogen value, commonly observed in similar systems when too small samples are employed, could not be repeated because the sample was exhausted.

(22%) of light tan needles which were recrystallized from cyclohexane and finally sublimed to give a colorless solid, m.p. 118°.

Anal. Calcd. for $C_{12}H_{19}N_5$: C, 61.77; H, 8.21; N, 30.02. Found: C, 61.48; H, 8.00; N, 30.55.

4-(3-Dimethylaminopropyl)amino-5-methylpyrrolo-[2,3-d]pyrimidine (**30**). A solution of 0.1 g. of 3-(3-dimethylaminopropyl)-4(3*H*)-imino-5-methylpyrrolo-[2,3-*d*]pyrimidine in 10 ml. of water was heated under reflux for 1 hr., cooled, and filtered to give 0.08 g. of product (80%) which was recrystallized from water containing a trace of ethanol to give white crystals, m.p. 170–172°.

Anal. Calcd. for $C_{12}H_{19}N_5$: C, 61.77; H, 8.21; N, 30.02. Found: C, 61.59; H, 7.80; N, 30.15.

3-Methyl-4(3H)-imino-5-phenylpyrrolo(2,3-d)pyrimidine (**28**). Treatment of 3.1 g. of 2-amino-3-cyano-4-phenylpyrrole with triethyl orthoformate followed by ethanolic methylamine, as described above for the 5-methyl analog **26**, gave 1.45 g. (38%) of crude product which was recrystallized from ethanol to give white crystals, m.p. 286.5–288°.

Anal. Calcd. for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.99. Found: C, 69.76; H, 5.82; N, 25.13.

4-Methylamino-5-phenylpyrrolo[2,3-d]pyrimidine (**31**). A solution of 0.2 g. of 3-methyl-4(3H)-imino-5-phenylpyrrolo[2,3-*d*]pyrimidine in 20 ml. of hot ethanol was diluted with water until incipient turbidity, heated under reflux for 13 hr., and evaporated to dryness under reduced pressure. The residue was extracted with hot ethanol; the small amount of solid which separated upon cooling was discarded, and the filtrate was diluted with water. The fine white needles which separated (0.1 g., 50%) were recrystallized from aqueous ethanol to give the analytical sample, m.p. 218–219.5°.

Anal. Calcd. for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.99. Found: C, 69.59; H, 5.40; N, 25.37.

Amide–Amide Reaction *via* Cyclols[1]

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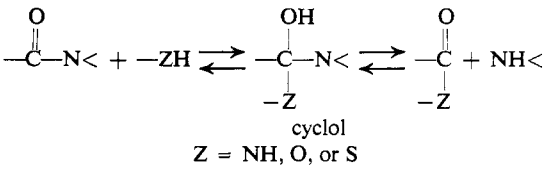
Of the many recent examples of cyclols and cyclol intermediates, one type lacking was that resulting from amide–amide reaction. The most favorable geometry for finding such a reaction appeared to be present in 6,10-dioxo-1,5-diazacyclodecane and 5,10-dioxo-1,6-diazacyclodecane where the forced amide juxtaposition might lead to transannular cyclolization. To prepare these compounds, rearrangement of the dioxime ditosylate of 1,5-cyclooctanedione was investigated and found to give only the unsymmetrical product. The same compound was prepared from N-(3-aminopropyl)glutarimide via cyclolization. Similarly, the symmetrical isomer was prepared from 1-(4-aminobutyryl)-2-pyrrolidinone. Each isomer, in acid, was converted to the substituted glutarimide and pyrrolidinone, respectively. The reactions could be easily reversed at pH 8, and occurred more readily with 6,10-dioxo-1,5-diazacyclodecane (6,6-fused ring cyclol) than with 5,10-dioxo-1,6-diazacyclodecane (5,7-fused ring cyclol). Both isomers gave mass spectral fragmentation patterns best rationalized through cyclol and transannular intermediates.

Introduction

The cyclol hypothesis, in its broadest sense, postulates a reaction between an amide, or other acyl derivative, and an –OH-, –SH-, or >NH-containing group as in the general expression



Attack at the carbonyl leads to the intermediate cyclol, which may then collapse to products. As originally advanced by Wrinch,[4] its purpose was to provide additional bonding and transformations in proteins.

The first clear experimental demonstration of such a reaction was furnished by the synthesis of ergotamine[5] which established the validity of a cyclol structure[6] in the peptide portion of this alkaloid. Since then, numerous examples have appeared of amide–amine, amide–alcohol, and amide–ester reactions,[7–11] including the synthesis of large-ring depsipeptides by cyclolization of β-hydroxypropionyldiketopiperazines.[12]

(1) This research was supported in part by the U. S. Army Research Office, Durham, N. C.
(2) National Institutes of Health Predoctoral Fellow.
(3) National Science Foundation Predoctoral Fellow.

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