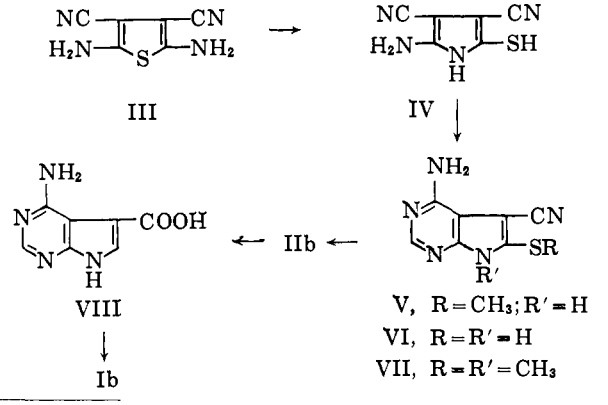
soil near Fuji City, Shizuoka Prefecture,[9] is reported to be active against *Mycobacterium tuberculosis* $H_{37}Rv$ and *Candida albicans*.[8] It has been shown to have structure IIa on the basis of spectral evidence and degradation.[9,10] Tubercidin has not been synthesized,[5,11] even though its aglycone Ib is a known compound.[7] The aglycone IIb of Toyocamycin is not known; it was not prepared from the antibiotic and has not been synthesized, presumably because the only previously available synthetic route to pyrrolo[2,3-*d*]pyrimidines, that discussed by Davoll[7] *via* pyrimidine intermediates, is not applicable to the preparation of 4-amino-5-cyanopyrrolo[2,3-*d*]pyrimidine (IIb).

We wish to describe in this communication a simple synthesis of the pyrrolo[2,3-*d*]pyrimidine ring system utilizing *pyrrole* intermediates which has permitted the preparation of the aglycones Ib and IIb of both antibiotics.[12]

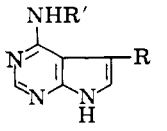
Tetracyanoethylene was converted by the action of hydrogen sulfide to 2,5-diamino-3,4-dicyanothiophene (III), which was rearranged with alkali to 5-amino-3,4-dicyano-2-mercaptopyrrole (IV) as described by Middleton, *et al.*[13] Treatment of IV with methyl orthoformate followed by alcoholic ammonia gave 4-amino-5-cyano-6-methylmercaptopyrrolo[2,3-*d*]pyrimidine[14] [V, m.p. 317–318° dec., 57% yield, $\lambda_{max}^{C_2H_5OH}$ 231 mμ (ε 16,500) and 301 (17,600); infrared, CN band at 2225 cm.$^{-1}$]. Desulfurization of V with Raney nickel[15] in aqueous ammonium hydroxide then gave 4-amino-5-cyanopyrrolo[2,3-*d*]pyrimidine [IIb, m.p. > 360°, 35% yield; $\lambda_{max}^{C_2H_5OH}$ 226 mμ (ε 10,700), 277 (13,700), 287 (9750)[16]; infrared, CN band at 2225 cm.$^{-1}$], the aglycone of Toyocamycin.

Alternatively, refluxing IV with formamidine acetate[17] in 2-ethoxyethanol gave 4-amino-5-cyano-6-mercaptopyrrolo[2,3-*d*]pyrimidine (VI), which was characterized as its 6,7-dimethyl derivative (VII, m.p. 315–317° dec.) by treatment with methyl iodide and alkali. Analogous methylation of V also gave VII. Raney nickel desulfurization of VI then gave IIb.

Confirmation of the structure of IIb was obtained by hydrolysis with 6 *N* hydrochloric acid to the corresponding 5-carboxylic acid [VIII, m.p. (as hydrochloride salt) 286–287° dec.; $\lambda_{max}^{0.1\ N\ HCl}$ 228 mμ (ε 10,380), 240 sh. (9050), 274 (11,120); $\lambda_{max}^{0.1\ N\ NaOH}$ 226 mμ (ε 10,280), 259 (9480), 280 (10,950)], followed by decarboxylation of its copper salt in quinoline[18] at 210° to give the known 4-aminopyrrolo[2,3-*d*]pyrimidine (Ib),[4,7] the aglycone of Tubercidin. This degradation of IIb thus constitutes an independent synthesis of Ib.



We wish to report at this time another but related pyrrolo[2,3-*d*]pyrimidine synthesis *via* pyrrole intermediates. The condensation of aminoacetone and of ω-aminoacetophenone (as representative examples of α-aminoketones) with malononitrile to give 5-amino-4-cyano-3-methyl- and 3-phenylpyrrole has recently been reported by Gewald.[19] We have found that these *o*-aminonitriles can be converted to 4-amino-5-methylpyrrolo[2,3-*d*]pyrimidine (IX, m.p. 257–258°, 50% yield) and 4-amino-5-phenylpyrrolo[2,3-*d*]pyrimidine (X, m.p. 259–261°, 35% yield), respectively, by initial reaction with ethyl orthoformate to give the 5-ethoxymethyleneamino derivatives, followed by treatment with alcoholic ammonia to give the 4-cyano-5-formamidino derivatives and final cyclization with sodium methoxide in methanol. Several 4-substituted amino derivatives of 5-methyl- and 5-phenylpyrrolo-[2,3-*d*]pyrimidine were prepared directly by reaction of the above 5-ethoxymethyleneamino intermediates with primary amines[20] (XI, m.p. 250–251.5°, 35% yield; XII, m.p. 124–127°, 19% yield; XIII, m.p. 286.5–288°, 38% yield). It would appear that appropriate combinations of the above two synthetic routes should make readily available a wide variety of 4-aminopyrrolo[2,3-*d*]pyrimidines structurally related to Tubercidin and Toyocamycin.



IX, R = CH_3; R' = H
X, R = C_6H_5; R' = H
XI, R = R' = CH_3
XII, R = CH_3; R' = $(CH_2)_3N(CH_3)_2$
XIII, R = C_6H_5, R' = CH_3

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(11) Y. Mizuno, M. Ikehara, K. A. Watanabe, and S. Suzaki, *J. Org. Chem.*, **28**, 3331 (1963).
(12) The preparation of Toyocamycin by ribosidation of IIb is under investigation.
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(14) Satisfactory microanalyses were obtained for all new compounds reported.
(15) D. J. Brown, *J. Soc. Chem. Ind.* (London), Part II, **69**, 353 (1950).
(16) Toyocamycin is reported (ref. 8, 9) to exhibit ultraviolet maxima (in methanol) at 230 and 279 mμ.
(17) E. C. Taylor and W. A. Ehrhart, *J. Am. Chem. Soc.*, **82**, 3138 (1960).
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(20) E. C. Taylor and P. K. Loeffler, *J. Am. Chem. Soc.*, **82**, 3147 (1960).
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Free-Radical Phenylation of Ferricenium Ion

Sir:

Although it is generally conceded that phenyl radicals are produced during interaction of ferrocene and benzenediazonium salts[1–5] there is a diversity of opinion as to the precise mechanism of the phenylation reaction. Several groups of workers[2,4,6] have supported Pauson's suggestion[1] that ferricenium ion and phenyl radicals are formed by an electron-transfer reaction as follows (FcH = ferrocene).

$$FcH + PhN_2^+ \longrightarrow FcH^+ + PhN_2\cdot \quad (1)$$

$$PhN_2\cdot \longrightarrow Ph\cdot + N_2 \quad (2)$$

However, the accompanying hypothesis[1] that free

(1) P. L. Pauson, *Quart. Rev.* (London), **9**, 391 (1955).
(2) W. F. Little and A. K. Clark, *J. Org. Chem.*, **25**, 1979 (1960).
(3) A. N. Nesmeyanov, E. G. Perevalova, and R. V. Golovnya, *Dokl. Akad. Nauk SSSR*, **97**, 459 (1954).
(4) M. Rosenblum, W. G. Howells, A. K. Banerjee, and C. Bennett, *J. Am. Chem. Soc.*, **84**, 2726 (1962).
(5) W. F. Little, K. N. Lynn, and R. Williams, *ibid.*, **85**, 3055 (1963).
(6) A. L. J. Beckwith and R. J. Leydon, *Tetrahedron Letters*, **No. 6**, 385 (1963).

phenyl radicals generated in this manner attack the neutral ferrocene molecule (eq. 3) seems improbable on energetic grounds,[7] and Little and Clark[2] accordingly formulated the phenylation reaction as proceeding by radical substitution of the ferricenium ion (eq. 4).

$$FcH + Ph\cdot \longrightarrow FcPh + H\cdot \quad (3)$$

$$FcH^+ + Ph\cdot \longrightarrow FcPh + H^+ \quad (4)$$

Recently, these suggestions have been discounted by Rosenblum and his co-workers,[4] who claim that neither ferrocene nor the ferricenium ion reacts with free phenyl radicals derived from phenylazotriphenylmethane, and who suggest that the mechanism of the phenylation reaction involves intermediate formation and intramolecular rearrangement of a ferrocene–diazonium salt charge-transfer complex. Nevertheless, the most recent work has demonstrated the high reactivity of ferricenium ion toward attack by free alkyl radicals[6] and has verified the production of free aryl radicals during the arylation reaction,[5,6] both of which observations provide indirect evidence for the mechanism suggested by Little and Clark.[2] In support of this mechanism we now describe the first unequivocal example of free-radical phenylation of ferricenium ion.

When ferricenium borofluoride (0.011 mole) and phenylazotriphenylmethane (0.011 mole) in acetic acid were maintained at 75° for 1.5 hr. nitrogen was evolved and the characteristic color of the ferricenium ion faded. The products isolated were phenylferrocene (0.002 mole) and triphenylcarbinol (0.006 mole) together with small amounts of tritylferrocene,[8] triphenylmethane, and tetraphenylmethane. Some ferrocene (0.004 mole) was recovered. Since it has been demonstrated previously that phenylazotriphenylmethane is without effect on neutral ferrocene,[4,6,9] there can be little doubt that the formation of phenylferrocene in the present instance represents an authentic example of free-radical phenylation of ferricenium ion.

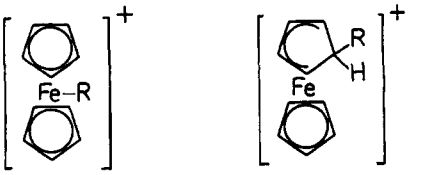
The mode of formation of tritylferrocene is less obvious. The production of triphenylcarbinol suggests that ferricenium ion and triphenylmethyl radical participate in the following oxidation–reduction equilibrium (eq. 5), the occurrence of which in the reverse direction has been observed earlier by Hawthorne.[10]

$$FcH^+ + Ph_3C\cdot \rightleftharpoons [FcHCPh_3]^+ \rightleftharpoons FcH + Ph_3C^+ \quad (5)$$

If, as seems possible, formation of tritylferrocene represents an alternative and irreversible mode of decomposition of the intermediate complex in the above equilibrium, it is no longer meaningful to distinguish between free-radical and electrophilic substitution in this system.

It may be significant that our experiment when carried out for 24 hr. afforded 1,1′-ditritylferrocene[8] but no triphenylcarbinol. Other products were unchanged.

Little[5] has suggested that either of the structures (I or II) may represent the intermediate complex in free-radical substitution of ferricenium ion. Both are of special interest in that, as drawn, they are identical with hypothetical intermediates in electrophilic substitution of the neutral ferrocene molecule.[11] Whether, in fact, free-radical and electrophilic substitution of ferricenium ion and ferrocene, respectively, proceed through the same intermediate, and whether this intermediate plays a part in oxidation–reduction equilibrium reactions (*e.g.*, eq. 5), are problems currently undergoing investigation in these laboratories.



I II

Ferricenium ion also undergoes substitution by free phenyl radicals generated oxidatively from phenylhydrazine.[12] When the latter (0.023 mole) was slowly added with stirring to the blue solution obtained by mixing ferrocene (0.007 mole) and silver oxide (0.022 mole) in acetic acid, phenylferrocene and 1,1′ diphenylferrocene were obtained in yields of 37% and 2% (based on unrecovered ferrocene), respectively. The yield of disubstituted product was increased to 9% when a large excess of phenylhydrazine and silver oxide was employed. In benzene the reaction proceeded less efficiently but the concomitant formation of biphenyl and terphenyl verified the presence of free phenyl radicals in the reaction mixture. Other oxidizing agents, *e.g.*, mercuric oxide, benzoquinone, also afforded phenylferrocene in small yield.

In view of the recent report[13] that oxidation of ferrocene with phenylmercuric acetate in the presence of perchloric acid affords phenyl radicals and ferricenium ion, we repeated this reaction in expectation of obtaining phenylferrocene. However, when the reactants were mixed in acetic acid–toluene, the only products were benzene and ferricenium ion and no phenylferrocene was formed. We were unable to detect bibenzyl and other compounds characteristically formed by attack of phenyl radicals on toluene.[14] Also, the reported formation of benzene *in quantitative yield* in this reaction is inconsistent with a free-radical mechanism. It thus appears that reduction of phenylmercuric acetate with ferrocene does not involve generation of free phenyl radicals.

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(11) M. Rosenblum, J. O. Santer, and W. G. Howells, *J. Am. Chem. Soc.*, **85**, 1450 (1963).
(12) R. L. Hardie and R. H. Thomson, *J. Chem. Soc.*, 2512 (1957).
(13) C. H. Wang, *J. Am. Chem. Soc.*, **85**, 2339 (1963).
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The Chemistry of Cleavamine: A Novel Transannular Cyclization Relating to Biosynthesis of Aspidosperma Alkaloids

Sir:

Recently, in connection with our interests in alkaloids from *Vinca rosea* Linn, we established the structure of cleavamine (I)[1] as one of the acid rearrangement products of catharanthine.[2] The close structural relationship of cleavamine to the known alkaloid quebrachamine[3] suggested its use as an excellent model for evaluating some of the reactions proposed in the biosynthesis of Aspidosperma alkaloids.

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(2) N. Neuss and M. Gorman, *Tetrahedron Letters*, 206 (1961).
(3) K. Biemann and G. Spiteller, *J. Am. Chem. Soc.*, **84**, 4578 (1962), and references cited therein.