Acknowledgment. This research has been supported by the Division of Chemical Sciences, Office of Basic Energy Sciences, U.S. Department of Energy (Report DOE/ER/02968-137). We thank Dr. S. Steenken for stimulating our interest in aliphatic ether radical cations.

Supplementary Material Available: The solid-state ESR spectrum of $(CH_3)_2O^+$ at 155 K (1 page). Ordering information is given on any current masthead page.

On the Nature of the Intermediate between 4a-Hydroperoxyflavin and 4a-Hydroxyflavin in the Hydroxylation Reaction of *p*-Hydroxybenzoate Hydroxylase. Synthesis of 6-Aminopyrimidine-2,4,5(3*H*)-triones and the Mechanism of Aromatic Hydroxylation by Flavin Monooxygenases

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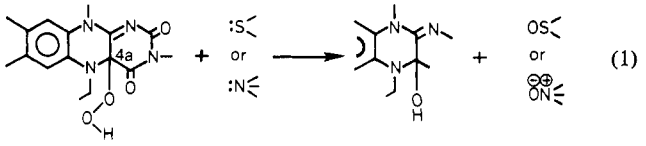
There appears to be a consensus that the reactions of reduced flavoenzyme monooxygenases with molecular oxygen provide enzyme-bound 4a-hydroxyperoxyflavin (4a-FlHOOH).[1-4a] In the N- and S-oxidation of amines by hepatic microsomal flavomonooxygenase,[5,6] substrate oxidation is accompanied by the conversion 4a-FlHOOH → 4a-FlHOH. The mechanism of the enzymatic reaction[7] appears to be identical in essential features with the bimolecular N- and S-oxidations with authentic 4a-hydroperoxyflavins (reaction 1).[2b,f,i] No evidence for intermediates



(4a-FlEtOOH) (4a-FlEtOH) (1)

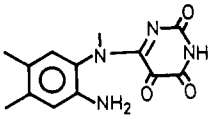
could be obtained, and the reactions are quantitative.[2i,7] In contrast, the mechanisms for bacterial hydroxylases responsible for hydroxylation of electron-rich aromatic compounds are poorly understood. The enzyme *p*-hydroxybenzoate hydroxylase serves as the most useful example for this class of enzymes.[8]

A strongly absorbing species (X) is formed from 4a-FlHOOH during the hydroxylation of a number of alternate substrates by *p*-hydroxybenzoate hydroxylase.[8] The disappearance of X is accompanied by the appearance of a species to which a 4a-hydroxyflavin structure (4a-FlHOH) was assigned (reaction 2).

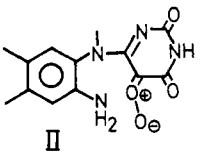
4a-FlHOOH ⟶ X ⟶ 4a-FlHOH

λ_{max} 380-390 nm, ϵ ~9000 M^{-1} cm^{-1} | λ_{max} 390-420 nm, ϵ ~15 000 M^{-1} cm^{-1} | λ_{max} 380-385 nm, ϵ ~9000 M^{-1} cm^{-1} (2)

The aromatic hydroxylation reaction differs, therefore, from the N< and S< oxidation reactions in which an intermediate (X) is not seen. The spectral observation of a well-defined intermediate occurring in time between 4a-FlHOOH and 4a-FlHOH is most important. Structure I has been assigned to X.[8] Massey and

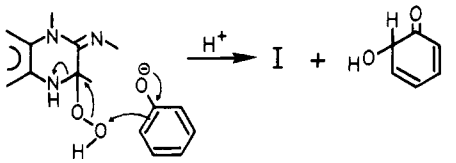


I



II

co-workers have proposed that I arises in concert with oxygen-atom transfer from 4a-FlHOOH to substrate (reaction 3).[8] Species



(3)

I was predicted by Hamilton[9] in 1971 as the immediate product of monooxygen transfer from his hypothetic carbonyl oxide II. Structures I and II have not only received a great deal of attention with respect to mechanism in flavomonooxygenase reactions, but structures completely analogous to I and II have been considered by Bailey and Ayling[10] to arise along the reaction paths for pteridine monooxygenases (responsible for initiation of the biosynthesis of neuroactive amines through hydroxylation of phenylalanine, tyrosine, and tryptophan). An assessment of the plausibility that X (reaction 3) = I, which has been disputed,[11] is most easily accomplished by independent synthesis of I and comparison of the spectral properties of X and I. The objective of this study has been to synthesize *N,N*-dimethyl-I (i.e., IX) and compare its spectral properties to those of X (reaction 2). 6-Amino-5-oxouracils (or 6-aminopyrimidine-2,4,5-triones) have not been isolated.[12,13] We describe herein our efforts to synthesize substituted 6-aminopyrimidine-2,4,5(3*H*)-triones from 5,6-diaminouracils and the first successful synthesis via 4a-5 ring opening of a suitably substituted flavin.

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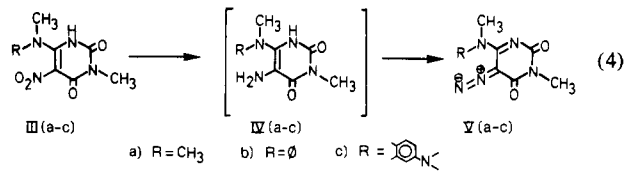
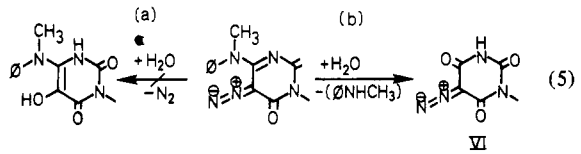
The three 5-diazo-6(*R*)-(methylamino)-3-methyluracils[14] **Va–c** were obtained by the sequence of reaction 4. In contrast to the



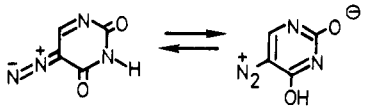
(4)

easy hydrolysis reported for 5-diazouracil,[21] compounds **Va–c** proved to be rather stable in acid solution. Hydrolysis of Vb yielded VI (IR 2180, 1745, 1720 and 1670 cm^{-1}; ^1H NMR 3.26 ppm) showing the extraordinary stability of the diazo group. The



(5)

difference in reactivity of V and 5-diazouracil may be related to the ability of the 5-diazouracil to tautomerize to an aromatic diazonium compound, a feature not allowed to V due to N(3) substitution. As already described by Sakuma and Yoneda,[16]



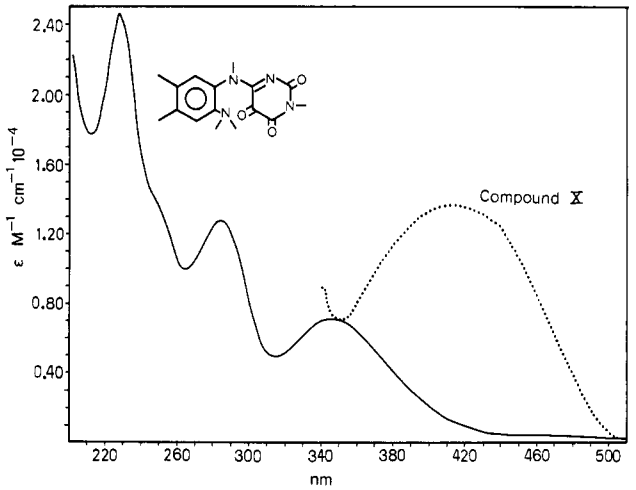
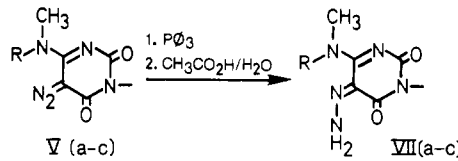


Figure 1. Comparison of the spectra of 6-[[2-(dimethylamino)-4,5-dimethylphenyl]methylamino]-3-methylpyrimidine-2,4,5(3*H*)-trione (IX) (—) and the intermediate X (···) observed with *p*-hydroxybenzoate hydroxylase (spectra of X computer digitized from: Ballou, D. P. Flavoprotein Monooxygenases, 7th International Symposium on Flavins and Flavoproteins, Ann Arbor, MI. Also see ref 8 of text).

the diazouracil Vb is converted to 3,9-dimethylpyrimido[4,5-*b*]-indole-2,3(1*H*,3*H*)-dione by both photochemical and thermal reactions. In addition, after heating with Cu(I) in 1 M aqueous HCl solutions, we obtained, again, the pyrimido[4,5-*b*]indole-2,3(1*H*,3*H*)-dione, while Cu(II) had no catalytical effect. Bestmann et al.[22] have described the synthesis of α,β-diketones by reacting α-diazoketones with triphenylphosphine followed by acid hydrolysis and reaction of the resulting hydrazone with sodium nitrite. Using a method analogous to Bestmann et al.[22] the three hydrazones VIIa–c[23] could be obtained. However, hydrolysis of



(6)

the hydrazones (VII) to the triones could not be effected. No reaction occurred on treatment of VIIa with NO_2^- in dioxane/1 M H_2SO_4. Similar treatment of VIIb provided 3,10-dimethylisoalloxazine N^5 oxide and 3,10-dimethylisoalloxazine, as established by comparison with authentic materials. As already known in the case of α-ketohydrazones,[22] compounds VII show great stability in aqueous acids so that treatment with acid alone was also unsuccessful.

(14) The 5-nitrouracils IIIa–c[15] were hydrogenated in aqueous solution over Pd on charcoal. After addition of 6 M sulfuric acid to make the solutions about 1 M, the catalyst was filtered off, and an excess of sodium nitrite was added. After 1 h and partial neutralization, the diazouracils Va–c were extracted with chloroform and precipitated with diethyl ether. Pure compounds were obtained by column chromatography on silica gel with chloroform or ethyl acetate as eluants. 5-Diazo-6-(dimethylamino)-3-methyluracil (Va): $C_7H_9N_5O_2$ (M_r 195.18); mp 136–140 °C dec; IR (KBr) 2130 (N_2), 1675 (C(4)=O), 1625 (C(2)=O), 1560 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.21 (s, 6 H, C(6)N(CH_3)$_2$); 3.10 (s, 3 H, N(3)CH_3). 5-Diazo-3-methyl-6-methylphenylaminouracil (Vb) has already been synthesized by Sakuma and Yoneda:[16] $C_{12}H_{11}N_5O_2$ (M_r 257.25); mp 178–180 °C dec (lit. 185 °C dec); IR (KBr) 2200 (w), 2140, 2110 (N_2), 1690 (C(4)=O), 1640 (C(2)=O), 1540, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57–7.12 (m, 5 H, ArH_5), 3.48 (s, 3 H, N(6)CH_3), 3.24 (s, 3 H, N(3)CH_3). 5-Diazo-6-[[2-(dimethylamino)-4,5-dimethylphenyl]methylamino]-3-methyluracil (Vc): $C_{16}H_{20}N_6O_2$ (M_r 328.37); mp 180–182 °C dec; IR (KBr) 2130 (N_2), 1695 (C(4)=O), 1645 (C(2)=O), 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (s, 1 H) and 6.69 (s, 1 H, C(3,6)H_2), 3.50 (s, 3 H, C(6)NCH_3), 3.32 (s, 3 H, N-(3)CH_3), 2.72 (s,6 H), C(2)N(CH_3)$_2$), 2.30 (s, 3 H) and 2.19 (s, 3 H, C(4,5)(CH_3)$_2$). Anal. Calcd: C, 58.52; H, 6.14; N, 25.60. Found: C 58.34; H, 6.29; N, 25.30.

(15) 6-(Dimethylamino)-3-methyl-5-nitrouracil (IIIa)[17b] and 3-methyl-6-(methylphenylamino)-5-nitrouracil (IIIb)[18] were prepared as described in the literature by condensation of 6-chloro-3-methyl-5-nitrouracil[17] with dimethylamine or phenylmethylamine. 6-[[2-(Dimethylamino)-4,5-dimethylphenyl]methylamino]-3-methyl-5-nitrouracil (IIIc) was prepared by analogous condensation with *N,N,N*,4,5-pentamethylphenylenediamine:[19] $C_{16}H_{21}N_5O_4$·H_2O (M_r 365.38). Anal. Calcd: C, 52.59; H, 6.34; N, 19.17. Found: C 52.75%; H 6.04%; N 19.08%.

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(19) Prepared by hydrolysis of *N*-formyl-*N,N',N'*,4,5-pentamethylphenylenediamine[20] in 3 M sulfuric acid and extracted with chloroform after neutralization: yellow oil, ^1H NMR ($CDCl_3$) δ 6.83 (s, 1 H) and 6.43 (s, 1 H, C(3,6)H_2), 2.84 (s, 3 H, (C(1)NCH_3), 2.63 (s, 6 H, C(2)N(CH_3)$_2$, 2.23 (s, 3 H) and 2.17 (s, 3 H, C(4,5)(CH_3)$_2$).

(20) Synthesized analogous to *N*-formyl-*N,N',N'*-trimethylphenylenediamine from 4,5-dimethylphenylenediamine by following the procedure of: Sekiya, M.; Tomie, M.; Leonard, N. J. *J. Org. Chem.* **1968**, *33*, 318. The compound has already been prepared via a different route by: Saito, I.; Abe, S.; Takahashi, Y.; Matsuura, T. *Tetrahedron Lett.* **1974**, 4001.

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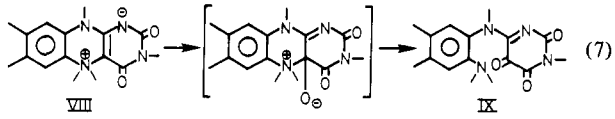
(23) The 5-diazouracils Va–c were dissolved in dry dioxane, and an excess of triphenylphosphine was added. After stirring for 1 h, the reaction mixture was poured into 0.3 M acetic acid. Following stirring for 30 min, the products were extracted with chloroform and purified via column chromatography on silica gel using ethyl acetate as eluant: 6-(Dimethylamino)-3-methylpyrimidine-2,4,5(3*H*)-trione-5-hydrazone (VIIa): $C_7H_{11}N_5O_2$·$^1/_8H_2O$ (M_r 199.45); mp 214 °C dec; IR (KBr) 3250 (NH); 1650 (C(4)=O); 1620 (C(2)=O) cm^{-1}; ^1H NMR ($CDCl_3$ + 10% CF_3CO_2H) δ 3.68 (s, 3 H), 3.54 (s, 3 H), 3.36 (s, 3 H). Anal. Calcd: C, 42.15; H, 5.68; N, 35.11. Found: C, 42.00; H, 5.55; N, 34.44. 3-Methyl-6-(methylphenylamino)pyrimidine-2,4,5(3*H*)-trione-5-hydrazone (VIIb): $C_{12}H_{13}N_5O_2$·$^1/_4H_2O$ (M_r 261.75) mp 141–146 °C dec; IR (KBr) 3350 (NH), 1680 (C(4)=O), 1640 (C(2)=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.00 (m, 5 H, Ph), 3.57 (s, 3 H), C(6)NCH_3), 3.30 (s, (N(3)CH_3). Anal. Calcd: C, 54.60; H, 5.15; N, 26.55. Found: C, 54.73; H, 5.15; N, 25.86. 6-[[2-(Dimethylamino)-4,5-dimethylphenyl]-methylamino]-3-methylpyrimidine-2,4,5(3*H*)-trione-5-hydrazone (VIIc): $C_{16}H_{22}N_6O_2$ (M_r 330.38) mp 162–164 °C dec; IR (KBr) 3300, 3350 (NH), 1680 (C(4)=O), 1640 (C(2)=O), 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (s, 2 H), (C(3,6)H_2), 3.44 (s, 3 H, C(6)NCH_3), 3.28 (s, 3 H, N(3)CH_3), 2.63 (s, 6 H), C(2)N(CH_3)$_2$), 2.23 (s, 1 H), and 2.15 (s, 3 H, C(4,5)(CH_3)$_2$). Anal. Calcd: C, 58.16; H, 6.71; N, 25.44. Found: C, 57.96; H, 6.81; N, 25.19.

A suitable procedure for the synthesis of the desired trione (IX) was found in the reaction of 3,5,5-trimethyl-1,5-dihydrolumiflavin[24] (VIII) with a stoichiometric amount of *m*-chloroperbenzoic acid in $CHCl_3$ (followed by washing with aqueous $NaHCO_3$ solution and column chromatography on silica with $CHCl_3$ as eluant). By this means, IX was obtained in moderate yield (~20%). The



(7)

VIII IX

structure of IX is proven by elemental analysis and IR, ^1H NMR, and finally ^{13}C NMR spectroscopy.[25] It represents the first isolated 6-aminopyrimidine-2,4,5(3*H*)-trione and thereby ends speculations[11] concerning its properties. Elemental analysis shows that C(5)=O is not hydrated, which is confirmed by four ^{13}C signals between 163 and 154 ppm. An sp^3-hybridized C(5) would absorb at much higher field (~70 ppm; cf. Ghisla et al.[4a] and Benkovic et al.[4b]). When compound IX is put into aqueous solution, spectral changes show fast hydration and, at higher pH values, probably hydrolysis. These reactions will be subject to further investigation.

When 5-acetyl-3-methyl-1,5-dihydrolumiflavin[26] was treated with *m*-chloroperbenzoic acid, as in the case of VIII, again a new compound could be isolated.[27] In this case, the ^{13}C NMR spectrum shows a signal at 71 ppm, clearly indicating an sp^3-hybridized C(4a). We ascribe the 5-acetyl-4a-hydroxy-4a,5-dihydroflavin structure to the new product, although we cannot exclude a ring-opened hydrated form.

All attempts to convert the ketone IX with hydrazine to the hydrazone VIIc failed, which is not totally unexpected. Thus, alloxan (pyrimidine-2,4,5,6(1*H*,3*H*)-trione) oxidizes phenylhydrazine giving dialuric acid, nitrogen, and benzene.[28] We have not been successful in obtaining VII via condensation of IX with hydrazine salts, as described for alloxan.[29] The redox properties of IX, and its reactivity toward different carbonyl reagents and nucleophiles (amines and alcohols), are presently under investigation.

From our (preliminary) results, we can draw some conclusions of biological relevance. As our model (IX) is stable and does not "self-destruct" by intramolecular redox reactions, those arguments[11] against a 4a,5 ring opening during enzymatic catalysis are invalid. On the other hand, the UV spectrum of the model compound IX (λ_{max} 342 nm, ϵ 7120 M^{-1} cm^{-1}) clearly shows no resemblance to the spectrum of the enzyme-bound X (λ_{max} 390–420 nm, ϵ 15 000 M^{-1} cm^{-1})[30] (Figure 1). This finding does not support the proposal that the pyrimidine-2,4,5(3*H*)-trione structure I represents X, and reaction 3 appears to have no experimental basis. There remains the possibility of X being the *p*- or *o*-quinoid tautomer of I: a 4-hydroxypyrimidine-2,4-dione or a 2-hydroxypyrimidine-4,5-dione. These two tautomers are expected to be less stable than I and, therefore, less probable. Nonetheless, efforts are under way in this laboratory to synthesize these tautomers. Finally, the fluorescence properties[31] of IX, unless drastically altered by the apoprotein, do not support its role as the emitter for bacterial luciferase.

Acknowledgment. This work was supported by grants from the National Science Foundation and the National Institutes of Health. We are very grateful to Professors J. J. Villafranca and S. J. Benkovic for the natural abundance ^{13}C NMR spectra.

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(25) 6-[[2-(Dimethylamino)-4,5-dimethylphenyl]methylamino]-3-methylpyrimidine-2,4,5(3*H*)-trione (IX): $C_{16}H_{20}N_4O_3$ (M_r 316.35); mp 230–235 °C dec; IR (KBr) 1720 (C(5)=O), 1700 (C(4)=O), 1665 (C(2)=O) cm^{-1}; UV (acetonitrile) λ_{max} (ϵ, M^{-1} cm^{-1}) 229 (24 600), 245 (sh), 281 (12 900), 342 (7120) nm; ^1H NMR ($CDCl_3$) δ 7.10 (s, 1 H) and 6.87 (s, 1 H, C(3′,6′)H_2), 3.60 (s, 3 H, C(6)NCH_3), 3.39 (s, 3 H, N(3)CH_3), 2.51 (s, 6 H, C(2′)N(CH_3)$_2$), 2.24 (s, 6 H, C(4′,5′)(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 162.7, 160.5, 159.7, 154.5 (C(2,4,5,6)), 139.2, 136.4, 136.4, 134.7, 124.9, 123.0 (C(1′,2′,3′,4′,5′,6′)), 43.0 (C(2′)N(CH_3)$_2$), 38.2 (C(6)NCH_3), 28.5 (N(3)CH_3), 19.6, 19.3 (C(4′,5′)(CH_3)$_2$). Anal. Calcd: C, 60.74; H, 6.37; N, 17.71. Found: C, 60.56; H, 6.43; N, 17.53.

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(27) 5-Acetyl-4a,5-dihydro-4a-hydroxy-3-methyllumiflavin or 6-[(2-(Acetylamino)-4,5-dimethylphenyl)methylamino]-3-methylpyrimidine-2,4,5-(3*H*)-trione hydrate: $C_{16}H_{18}N_4O_4 \cdot {}^4/_3H_2O$ (M_r 354.36); mp 185–190 °C dec (to 3-methyllumiflavin); IR (KBr) 3400, 3250 (OH), 1735 (C(4)=O), 1690 and 1660 (C(2)=O and N(5)C=O), 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (s, 1 H) and 7.01 (s, 1 H, C(6,9)H_2), 3.63 (s, 3 H, N(10)CH_3), 3.36 (s, 3 H, N(3)CH_3), 2.36 (s, 6 H, C(7,8)(CH_3)$_2$), 2.10 (s, 3 H, C(5)NCOCH_3); ^{13}C NMR ($CDCl_3$) δ 173.0 (N(5)$COCH_3$), 165.9, 162.1, 155.7 (C(2,4,10a)), 136.5, 133.1, 132.5, 127.5, 124.9, 117.5 (C(5a,6,7,8,9,9a)), 71.0 (C(4a)), 31.9 (N(10)CH_3), 27.6 (N(3)CH_3), 22.5 (N(5)$COCH_3$), 19.6, 19.2 (C(7,8)(CH_3)$_2$). Anal. Calcd: C, 54.23; H, 5.88; N, 15.81. Found: C, 54.13; H, 5.58; N, 15.58.

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(30) In fact, the UV data of IX resemble more those of 4a-hydroxy-4a,5-dihydroflavins (cf. Ghisla, S.; Entsch, B.; Massey, V.; Husein, M. *Eur. J. Biochem.* **1977**, *76*, 139), which should lead to caution in ascribing 4a-FlOH structures (cf. reaction 2) to enzyme-bound intermediates solely on the basis of UV data.

(31) Compound IX is nonfluorescent in solution (solvent acetonitrile) and shows only very weak fluorescence (λ_{max} ~410–430 nm; λ_{max} (excitation) 330–340 nm) in DMF/ethylene glycol dimethyl ether glass at 77 K. Whether an excited state of IX can transfer its energy to another fluorescer (as proposed for a model reaction[2k]) will be subject to further investigation.

Intercalation of Potentially Reactive Transition-Metal Complexes in the Lamellar $MnPS_3$ Host Lattice

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The increasing interest in intercalated layer systems has remained largely centered, during the past years, on those systems exhibiting electrical conductivity.[1] Molecular reactions in the interlayer space are an attractive topic for research; recently, several novel organic reactions have been carried out in the interlayer space of layered silicates.[2-5] The catalytic[6,7] and photocatalytic[8,9] properties of organometallic intercalated silicates are also of great potential interest. This communication describes the synthesis of new intercalation compounds based on $MnPS_3$ host layers, containing large cationic species potentially suitable for further chemistry or photochemical experiments.

$MnPS_3$ belongs to a class of lamellar semiconducting materials[10] known, as the structurally analogous transition-metal dichalcogenides, to intercalate electron-donor species, such as amines[11] or cobaltocene.[12] It has been recently shown that $MnPS_3$

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