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# SYNTHESIS AND TRYPANOCIDAL ACTIVITY OF THE BIS-CARBA ANALOGUE OF PENTAMIDINE

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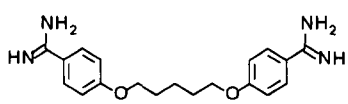
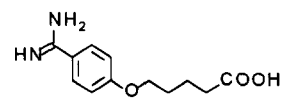
**Abstract:** Because toxic metabolites are formed by microsomal oxidative cleavage of the ether methylenes of the antiprotozoal drug, pentamidine, we synthesized the previously unreported analogue of pentamidine in which the ether oxygens are replaced by methylenes. Although this compound was about 20-fold less active than pentamidine against *Trypanosoma brucei* infection in mice, it did not undergo oxidative cleavage, suggesting a new direction for design of less toxic pentamidine analogues. 

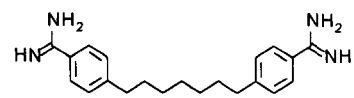
Pentamidine, a trypanocidal drug developed almost 60 years ago, has recently become of renewed importance because of its activity against *Pneumocystis carinii* pneumonia in AIDS and immunosuppressed patients. Even in the currently used aerosol formulation, pentamidine has significant toxicity, which can lead to kidney damage and pancreatic beta-cell damage. Recent work has indicated that a microsomal oxidative cleavage product of pentamidine, the amidinophenoxy acid **1**,[1] can cause kidney necrosis in rats.[2] We therefore decided to synthesize and test the previously undescribed bis-carba analogue of pentamidine, 1,7-bis(4-amidinophenyl)heptane (**2**), which should be less likely to form a metabolite resembling **1**.




**Pentamidine**




**1**




**2**

Synthesis of **2** proceeded from the known[3] 1,7-bis(4-bromophenyl)heptane by reaction with copper(I) cyanide pyridine complex at 215—225 °C for 15 h. The resulting 1,7-heptanediylbis(4-benzonitrile)[4] was treated with anhydrous HCl in dioxane-ethanol at 25 °C for 3 days. The crude diethyl 1,7-heptanediylbis(4-benzimidate) dihydrochloride was isolated and treated with anhydrous $NH_3$ in ethanol at 25 °C for 3 days to

yield **2** as the dihydrochloride.[5] This procedure would be easily adaptable to produce analogues of varying chain length, as other homologous α,ω-bis(4-bromophenyl)alkanes are readily available.[3]

Incubation of **2** with rat liver microsomes under conditions described previously for pentamidine[1] produced metabolites with chromatographic properties consistent with hydroxylation products at the 2, 3, or 4 positions of the alkane chain, but no peaks consistent with chain cleavage products.

Compound **2** was compared with pentamidine for 30-day curative activity when administered ip 24 h after ip inoculation with $10^4$ *Trypanosoma brucei brucei* S427/118 organisms. Compound **2** was about 20 fold less active ($ED_{50}$ = 7.3 ± 1.0 mg/kg) than pentamidine in this system ($ED_{50}$ = 0.38 ± 0.03 mg/kg) (Figure 1). Another non-ether-linked pentamidine-like derivative with an additional benzene ring, 1,4-bis(4-amidinophenylethyl)-benzene dihydrochloride, has also been reported to be about 20-fold less active than pentamidine against *T. brucei rhodesiense* infection in mice.[6]

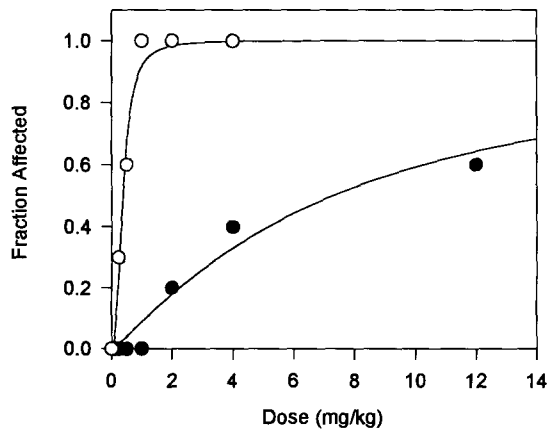



**Figure 1.** ○ = Pentamidine; ● = **2**

The loss of activity caused by replacement of the oxygens of pentamidine by methylenes may be due to an increase in lipophilicity in **2** relative to pentamidine, possibly leading to poor pharmacokinetics of transit from the peritoneum to the bloodstream. However, the absence of oxidative chain cleavage to metabolites resembling **1** suggests that **2** represents an interesting new direction toward designing pentamidine analogues of lower toxicity. Syntheses are currently underway of analogues of **2** directed toward improvement of its pharmacological properties.

## REFERENCES AND NOTES

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3. Kantor, S. W.; Sung, T.-C.; Atkins, E. D. T. *Macromolecules* **1992**, *25*, 2789.
4. mp 102 °C. $^1$H NMR ($CD_3OD$; 270 MHz) δ (ppm): 1.45 (6H, m), 1.75 (4H, m), 2.80 (4H, t) 7.45 (4H, d), 7.72 (4H, d).
5. mp 240 °C (dec.). Anal. Calcd for $C_{21}H_{30}Cl_2N_4$: C, 59.859; H, 7.763; N, 12.692. Found: C, 60.109; H, 7.678; N, 12.442. $^1$H NMR (DMSO-$d_6$, 270 MHz) δ (ppm): 1.40 (6H, m), 1.65 (4H, m), 2.75 (4H, t), 7.45 (4H, d), 7.85 (4H, d), ca. 7.3-7.9 (8H, br m). $^{13}$C NMR ($CD_3OD$) δ (ppm): 28.8, 29.0, 30.9, 35.5, 125.3, 127.7, 129.2, 150.0, 166.8.
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