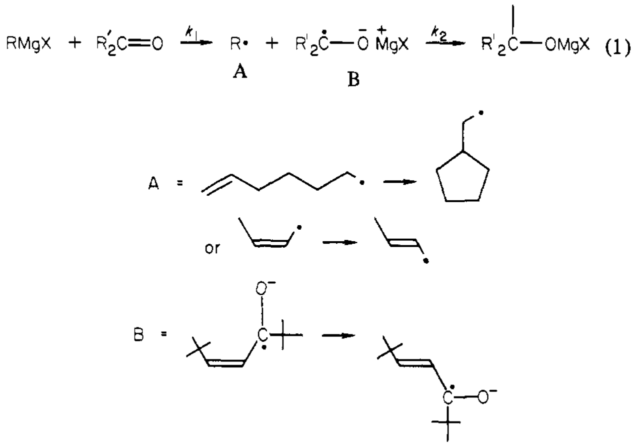
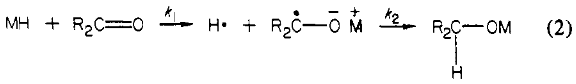


$$\mathrm{RMgX} + \mathrm{R'_2C{=}O} \xrightarrow{k_1} \underset{A}{\mathrm{R}\cdot} + \underset{B}{\mathrm{R'_2\dot{C}{-}\bar{O}\overset{+}{M}gX}} \xrightarrow{k_2} \mathrm{R'_2\overset{|}{C}{-}OMgX} \quad (1)$$



$$\mathrm{MH} + \mathrm{R_2C{=}O} \xrightarrow{k_1} \mathrm{H}\cdot + \mathrm{R_2\dot{C}{-}\bar{O}\overset{+}{M}} \xrightarrow{k_2} \mathrm{R_2\underset{H}{\underset{|}{C}}{-}OM} \quad (2)$$

in THF, a violet color (λ_{max} 579 nm) appears within a few minutes. This colored solution shows a complex EPR signal (Figure 1). The spectrum consists of several well-resolved peaks associated with a broad peak (or peaks), irrespective of the solution concentration (spectra were recorded for samples at 10^{-4}–10^{-2} M concentration). This behavior of the spectrum is probably due to the overlapping signals of radical anion and radical cation since no other signal could be observed in the region ($g = 2.003 \pm 4000$ G).

Both the intensity of the EPR signal and the visible absorption increase and reach a maximum, beyond which decay proceeds in a first-order fashion over a period of 3 days. By UV–vis spectroscopy it is observed that the intensity of the signal at λ_{max} 269 nm ($\epsilon \sim 12000$), due to the starting ketone, decreases rapidly as the signal due to the colored intermediate species (λ_{max} 579 nm) increases. The signal due to the ketone almost completely disappears in about 10 h for a reaction of 0.07 M concentration, indicating the irreversibility of this reaction. Beyond this time, the band due to the intermediate at 579 nm decreases in a first-order fashion at the same rate that the product is formed. Thus, an estimate of the concentration of the intermediate species can be made at any time from these results and at the maximum it has been calculated to be approximately 65%. A similar value of the concentration is obtained from the EPR calibration.[7]

The final outcome of the reaction is a 100% yield of reduction product. This reduction product is formed continuously during the entire course of reaction and arises in a first-order fashion after the EPR and visible absorption reach a maximum (Figure 2). This kinetic analysis indicates the presence of a paramagnetic intermediate on the reaction pathway for reduction. On the basis of these results, a probable mechanistic scheme (Scheme I) involving a relatively stable radical cation–radical anion pair as the intermediate is proposed. The unusually high stability of the intermediate (A) might lead one to conclude that it is the free ketyl; however, this alternate possibility can be excluded, as we have observed that the free ketyl prepared independently does not abstract hydrogen either from THF or from free metal hydride to give the reduction product. The first-order rate constant k_2 for the reaction of AlH_3 with DMK is 1.43×10^{-5} s^{-1} [R(correlation) 0.0996].

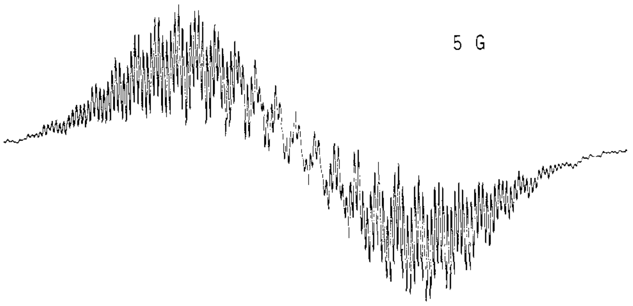


Figure 1. EPR spectrum of the reaction of AlH_3 with dimesityl ketone (0.07 M) in THF ($g = 2.0056$).

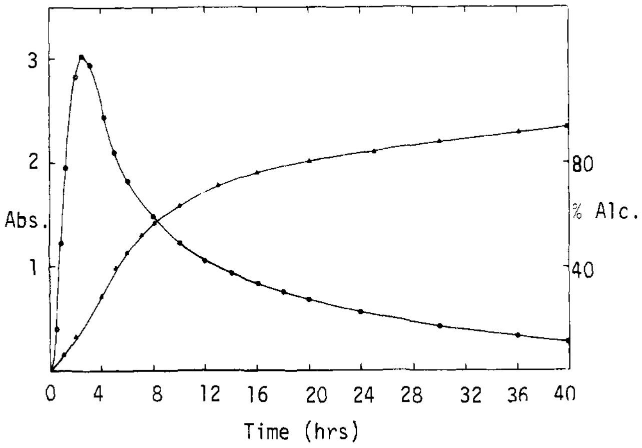
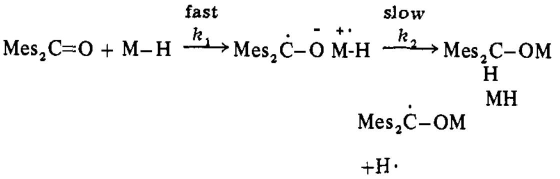


Figure 2. Reaction of AlH_3 with dimesityl ketone (0.07 M) in THF: (○) absorbance (λ_{max} 579 nm) vs. time; (△) product (%) vs. time (h).

Scheme I



$$\mathrm{Mes_2C{=}O} + \mathrm{M{-}H} \xrightarrow[\text{fast}]{k_1} \mathrm{Mes_2\dot{C}{-}\bar{O}\ \overset{+\cdot}{M}{-}H} \xrightarrow[\text{slow}]{k_2} \mathrm{Mes_2\underset{H}{C}{-}OM}$$
$$\mathrm{Mes_2\dot{C}{-}OM} \quad \mathrm{MH} \quad +\mathrm{H}\cdot$$

The reactions of MgH_2 and HMgX (X = Cl and Br) with DMK in THF also exhibit an intense EPR signal and strong visible absorption (λ_{max} 638 and 640 nm, respectively). The EPR signal observed for the intermediate of the reaction of HMgBr with DMK is found to be similar to that of the free ketyl generated from the reaction of DMK with t-BuMgBr. The kinetic behavior of the EPR signal and visible absorption for the magnesium hydrides is similar to that for AlH_3, but much slower. Again high yields of reduction product are obtained in each case. A visible absorption band (λ_{max} 638) and EPR signal is also observed for the reaction of $BH_3 \cdot THF$ and DMK, although the intensities are much less.

While the steric hindrance of DMK certainly allows the observation of an intermediate by slowing down the final step (k_2), the ET mechanism should be applicable to the reaction of other less hindered but more easily reducible ketones such as benzophenone, for which no stable intermediate is observed. We are now actively pursuing further characterization of the observable ET intermediate and extending the work reported here to other substrates and complex metal hydrides.

Eugene C. Ashby,* Anil B. Goel, Robert N. DePriest
School of Chemistry
Georgia Institute of Technology
Atlanta, Georgia 30332

Received July 9, 1980

---

[7] AlH_3 was prepared from the reaction of $LiAlH_4$ with M_2SO_4. The resulting solution was analyzed and found to be free of lithium ion.

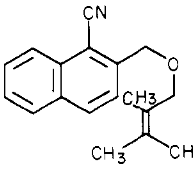
Naphthonitrile–Alkene Exciplexes. Use of Tethered Chromophores to Probe Geometric Factors in Exciplex Formation and Decay

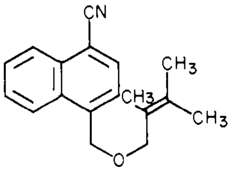
Sir:

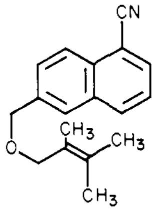
The aryl nitrile–olefin systems are interesting because they show exciplex fluorescence[1] as well as photoreactions. These allow

0002-7863/80/1502-7780$01.00/0

photophysics[2] and photochemistry[3] of singlet exciplexes to be studied. In particular, the role of exciplexes in 2 + 2 cycloaddition has been investigated.[3] Although exciplexes in photoadditions have been the subject of many studies,[3,4] it is only recently that experimental results[3d,4b,c] have been correlated by theory.[5] Geometric factors in aryl nitrile–alkene exciplex chemistry have not been investigated previously, and we now report our results with the bichromophoric[6] molecules **1**–**3**.


1


2


3

The important results are as follows: (i) compounds **1**–**3** all form internal exciplexes which fluoresce. Thus, formation of the *exciplex state is independent of position of attachement of the three-atom chain* to the naphthonitrile ring. (ii) Internal photoaddition of the alkene moiety to the naphthonitrile ring in **1** occurs with a much higher quantum yield than the bimolecular analogue, showing that the *three-atom chain has a profound effect on the efficiency with which the exciplex collapses to product.*

The fluoresence spectra of **1**–**3**[7] in ethyl acetate are shown in Figure 1.[8] The exciplex emission resembles the well-known fluoresence from bimolecular 1-naphthonitrile–alkene exciplexes.[1,2a,b] The monomer emission is approximately 95% quenched by the unsaturated side chain. Therefore, although the internal exciplexes are formed efficiently, their emission is weak.[9] In **2** and **3** the ethylene moiety cannot reach the 1,2-bond of the naphthonitrile. Since 2 + 2 photoadditions occur at the substituted double bond of naphthalene derivaties,[10] observation of exciplex fluorescence from **1**–**3** suggests that PMO theory should be used with caution in describing these complexes.[3d,11,12]

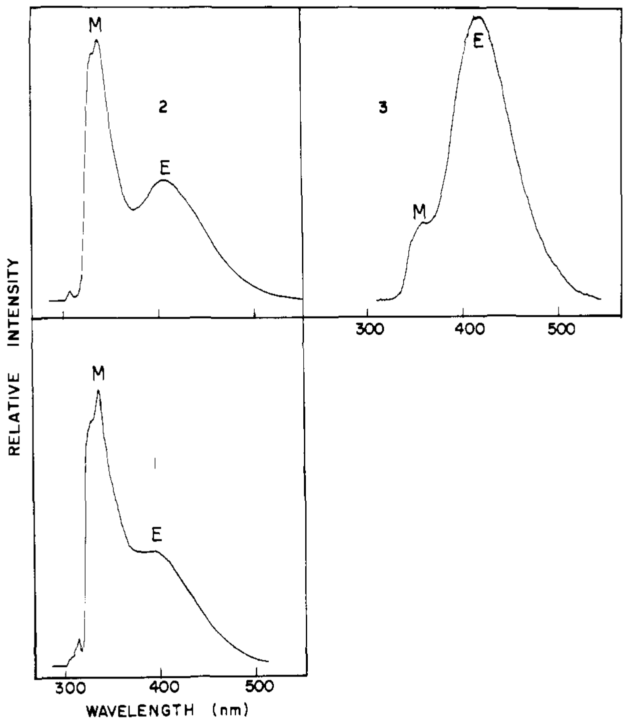


Figure 1. Fluorescence spectra of **1**, **2**, and **3** in ethyl acetate at 10^{-4} M monomer (M). Exciplex emission is visible with the latter at 418 (**1**), 428 (**2**), and 420 nm (**3**).

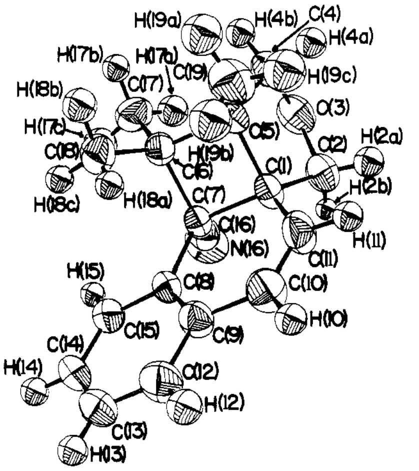


Figure 2. Structure of 7-cyano-5,6,6-trimethyl-8,9-benzo-3-oxatricyclo-$[5.4.0.0^{1,5}]$undeca-8,10-diene (**7**).

The photochemistry of **1** was compared with that of the biomolecular analogue. Irradiation of 2-methyl-1-naphthonitrile and tetramethylethylene (TME) (313 nm, benzene solvent) gives equal amounts of **4** and **5**.[13] Irradiation of TME with 4-methyl-1-naphthonitrile gives **6**.[13] Irradiation of **1** gives **7** and

---

[1] G. N. Taylor, *Chem. Phys. Lett.*, **10**, 355 (1971).

[2] (a) W. R. Ware, D. Watt, and J. D. Holmes, *J. Am. Chem. Soc.*, **96**, 7853 (1974); (b) D. V. O'Connor and W. R. Ware, *ibid.*, **98**, 4706 (1976); (c) *ibid.*, **101**, 121 (1979); (d) H. Ohta, D. Creed, P. H. Wine, R. A. Caldwell, and L. A. Melton, *ibid.*, **98**, 2002 (1976), and references cited.

[3] (a) K. Mizuno, C. Pac, and H. Sakurai, *J. Am. Chem. Soc.*, **96**, 2993 (1974); (b) R. A. Caldwell and L. Smith, *ibid.*, **96**, 2994 (1974); (c) J. J. McCullough, R. C. Miller, D. Fung, W.-S. Wu, *ibid.*, **97**, 5942 (1975); (d) R. A. Caldwell, N. I. Ghali, C.-K. Chein, D. DeMarco, and L. Smith, *ibid.*, **100**, 2857 (1978); (e) R. A. Caldwell and D. Creed, *ibid.*, **100**, 2905 (1978); (f) N. C. Yang, R. L. Yates, J. Masnovi, D. M. Shold, and W. Chiang, *Pure. Appl. Chem.*, **51**, 173 (1979).

[4] (a) P. Wells and H. Morrison, *J. Am. Chem. Soc.*, **97**, 154 (1975); (b) F. D. Lewis and C. E. Hoyle, *ibid.*, **99**, 3779 (1977); (c) R. C. Miller, Ph.D. Thesis, McMaster University, 1978.

[5] (a) J. Michl, *Photochem. Photobiol.*, **25**, 141 (1977); (b) R. A. Caldwell, *J. Am. Chem. Soc.*, **102**, 4004 (1980).

[6] Work with bichromophoric systems is currently an active research area. See: (a) F. C. DeSchryver, N. Boens, and J. Put, *Adv. Photochem.*, **10**, 359 (1977); (b) M. A. Winnik, *Acc. Chem. Res.*, **10**, 173 (1977); (c) R. S. Davidson and T. D. Whelan, *J. Chem. Soc., Chem. Commun.*, 361 (1977); (d) A. Gilbert and G. Taylor, *ibid.*, 129 (1978); (e) J. A. Ors and R. Srinivasan, J. Am. Chem. *Soc.*, **100**, 315 (1978); (f) K. Zachariasse and W. Kuhnle, *Z. Phys. Chem.* (*Wiesbaden*), **101**, 267 (1976); (g) K. Zachariasse, W. Kuhnle, and A. Weller, *Chem. Phys. Lett.*, **59**, 375 (1978); (h) T. Hayashi, N. Mataga, Y. Sakata, and S. Misumi, *ibid.*, **41**, 325 (1976); (i) M. Yoshida, H. Tatemitsu, Y. Sakata, S. Misumi, H. Masuhara, and N. Mataga, *J. Chem. Soc., Chem. Commun.*, 587 (1976); (j) T. Nylund and H. Morrison, *J. Am. Chem. Soc.*, **100**, 7364 (1978), and references therein; (k) J. P. Desvergne and H. Bouas-Laurent, *Isr. J. Chem.*, **18**, 220 (1979); (l) N. C. Yang, S. B. Neoh, T. Naito, L.-K. Ng, D. A. Chernoff, and D. B. McDonald, *J. Am. Chem. Soc.*, **102**, 2806 (1980).

[7] Preparation involved the Williamson ether synthesis, from the appropriate alcohols and halides; **1** had mp 55–56 °C, **2** had mp 43–44 °C, and **3** had mp 73–74 °C, after crystallization and sublimation. Spectral data and elemental analyses were in full agreement with the structures.

[8] The exciplex emission (*E*) persists at 10^{-5} M, which should preclude bimolecular complex formation.

[9] Compare R. S. Davidson and K. R. Trethewey, *J. Chem. Soc., Chem. Commun.*, 827 (1976).

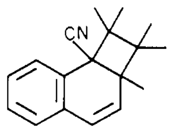
---

[10] T. R. Chamberlain and J. J. McCullough, *Can. J. Chem.*, **51**, 2578 (1973); J. J. McClullough, R. C. Miller, and W. S. Wu, *ibid.*, **55**, 2909 (1977), and references therein.

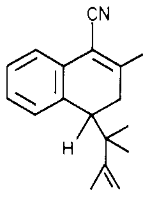
[11] F. D. Lewis, C. E. Hoyle, and D. E. Johnson, *J. Am. Chem. Soc.*, **97**, 3267 (1975).

[12] We have been unsuccessful so far in showing that the fluorescent exciplex is an intermediate in these additions and assume that it is. However, our substrates are structurally so similar to those of Caldwell[3d] that we are justified in making this assumption.

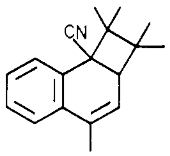
[13] **4** was an oil, **5** had mp 101–102 °C, and **6** had mp 93–94 °C. Structures were asssigned from spectral data and analyses, and by analogy with similar adduucts.[10]



4

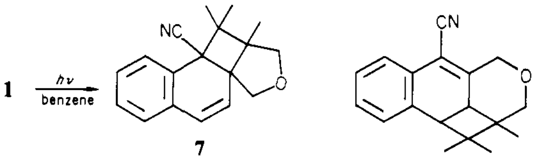


5



6

8, in the approximate ratio 20:1. The ratio was determined by GLC, and the compounds were separated by column chromatography.[14]



7

8

The structure of photoproduct 7, mp 141.5–142.5 °C, was established by single-crystal X-ray diffraction. Crystal data: $C_{18}H_{19}NO$, monoclinic, space group $P2_1/c$, C_{2h}^5 (No. 14), a = 12.088 (3) Å, b = 8.162 (2) Å, c = 15.152 (3) Å, Z = 4. A total of 2378 independent reflections in $2\theta_{\mathrm{Mo}\,K\alpha} \leq 55°$ was collected on a Syntex P2$_1$ automated diffractometer using the θ–2θ scan mode and graphite-monochromated Mo radiation. Initial coordinates for the nonhydrogen atoms were obtained by direct methods (MULTAN). Full-matrix least-squares refinement of the structural parameters and a scale factor, using anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms, led to R_1 = 0.064 and R_2 = 0.060.[15] Bond lengths and bond angles within the structure are normal. The structure is shown in Figure 2.

The structure of 8, mp 119–120 °C, was assigned from its spectra.[16] Important features are as follows: IR 2217 cm^{-1} (conjugated CN); ^{1}H NMR (FT, 80 MHz, CDCl$_3$) δ 7.0 (m, aromatics), 3.85, 2.95 (AB quartets, J = 9.8 Hz, area 2, bridgehead methines), centered at δ 3.73 (J = 10.0 Hz, area 2, allylic CH$_2$), centered at δ 3.15 (J = 5.0 Hz, area 2, CH$_2$). Methyl groups appeared at δ 0, 0.59, and 1.1 (s, each area 3).

Quantum yields of formation of the cycloadducts 4, 6, and 7 were measured.[17] Limiting quantum yields (infinite TME concentration) were 0.020 for 4 and 0.51 for 6. Thus, the methyl group in 2-methyl-1-naphtonitrile is exerting a significant steric effect on collapse of exciplex to product. The quantum yield for formation of 7 was 0.68. Since 1 is a 2-alkylnaphthonitrile, the much higher quantum yield of 7 vs. 4 shows that the order introduced in the reactant by the three-atom chain significantly favors exciplex collapse to product.

Exciplex decay and collapse to product should have the same activation energy,[5a] and indeed Caldwell has found that both are activated processes in several systems.[18] Clearly, the three-atom link in 1 must be influencing the choice which the system makes on crossing from the excited- to the ground-state surface at the pericyclic minimum.[19,20]

Acknowledgment. This work was supported by the Natural Science and Engineering Research Council of Canada.

---

(14) The technique of W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978), was employed.

(15) $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $R_2 = \{\sum w(|F_o| - |F_c|)^2/\sum wF_o^2\}^{1/2}$.

(16) Mass spectra and ^{13}C NMR spectra of 4–8 were also consistent with the assigned structures, and satisfactory analyses were obtained.

(17) Irradiation was at 313 nm, using a monochromator, beam splitter, and ferrioxalate actinometry. Product assay was by GLC (1.2 m × 4 mm of 3% OV-1 on 80/100 mesh WHP), using phenanthrene or 4,4′-dichlorobenzophenone as internal standard.

(18) R. A. Caldwell and D. Creed, *Acc. Chem. Res.*, **13**, 45 (1980), and references therein.

(19) Triplet formation does not account for the inefficiency in collapse of 2-methyl-1-naphthonitrile–TME exciplex. No triplets were detected from this system or from 1, using biacetyl phosphorescence as monitor.[20] Also, the efficiency of exciplex fluorescence is 0.1 or smaller.

(20) F. Wilkinson and J. T. Dubois, *J. Chem. Phys.*, **39**, 377 (1963).

(21) (a) Department of Chemistry; (b) Institute for Materials Research.

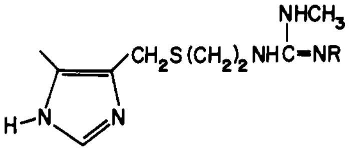
John J. McCullough,*[21a] W. Keith MacInnis[21a]
Colin J. L. Lock,[21a,b] Rommulo Faggiani[21b]
Department of Chemistry and
Institute for Materials Research
McMaster University
Hamilton, Ontario, Canada L8S 4M1

Received July 18, 1980

Copper(II) Complexes of the Antiulcer Drug Cimetidine

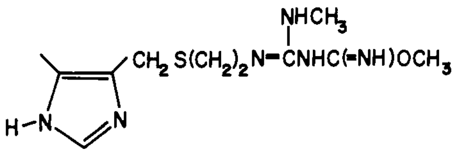
Sir:

One of the most potent histamine H$_2$ receptor antagonists is cimetidine (1), marketed under the trade name Tagamet,[1] which is used for the treatment of peptic ulcer.[2-4] The drug is taken



1 R = CN

2 R = CONH$_2$



3

orally and reaches the H$_2$ receptors via the blood stream. Since micromolar levels of loosely bound Cu(II) are present in blood serum,[5] the drug may exist as a Cu(II) chelate under in vivo conditions. This realization along with a report that Cu(II) dramatically increases specific cimetidine binding to rat brain histamine H$_2$ receptors[6] and the fact that certain Cu(II) coordination compounds show antiulcer activity prompted us to explore the copper binding properties of 1. We have found that the drug readily reacts with the cation to produce blue and green Cu(II) complexes. While the green compound contains the unaltered drug (1), the blue complexes possess forms of cimetidine which have been modified by a copper-catalyzed solvolysis (by water or methanol) of the nitrile function (2 and 3). In this report we describe the synthesis, spectroscopic characterization, and X-ray crystallographic analyses[8] of the green (4) and blue (5) Cu(II)

---

(1) Marketed by Smith, Kline and French, Philadelphia, PA.

(2) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. *J. Med. Chem.* **1977**, *20*, 901.

(3) Brimblecombe, R. W.; Duncan, W. A. M.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Parsons, M. E. *J. Int. Med. Res.* **1975**, *3*, 86.

(4) Ivey, K. J.; Baskin, W.; Jeffrey, G. *Lancet* **1975**, *2*, 1072.

(5) Perrin, D. D.; Agarwal, R. P. In "Metal Ions in Biological Systems"; Sigel, H., Ed.; Marcel Dekker: New York, 1973; Vol. 2, p 167.

(6) Kendall, D. A.; Ferkany, J. W.; Enna, S. J. *Life Sci.* **1980**, *26*, 1293.

(7) Sorenson, J. R. J. *Inflammation* **1976**, *1*, 317. Rainsford, K. D.; Whitehouse, M. W. *J. Pharm. Pharmacol.* **1976**, *28*, 83.

0002-7863/80/1502-7782$01.00/0