(3) I. J. Massey and I. T. Harrison, *Chem. Ind. (London)*, 920 (1977).
(4) C. Hansch, S. H. Unger, and A. B. Forsythe, *J. Med. Chem.*, **16**, 1217 (1973).
(5) F. Darvas, *J. Med. Chem.*, **17**, 799 (1974).
(6) S. H. Unger, J. R. Cook, and J. S. Hollenberg, *J. Pharm. Sci.*, in press.
(7) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, **16**, 1207 (1973).
(8) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).
(9) A. E. Hoerl and R. W. Kennard, *Technometrics*, **12**, 55 (1970).
(10) R. E. Buchanan and N. E. Gibbons, Ed., "Bergey's Manual of Determinative Bacteriology", 8th ed, Williams and Wilkins, Baltimore, Md., 1974, p 682.
(11) H. Bechgaard and C. Lund-Jensen, *Eur. J. Med. Chem.*, **10**, 103 (1975).
(12) K. Bowden and M. P. Henry, *Adv. Chem. Ser.*, **114**, 130 (1972).
(13) C. Hansch and E. W. Deutsch, *J. Med. Chem.*, **8**, 705 (1965).
(14) K. H. Büchel and W. Draber, *Adv. Chem. Ser.*, **114**, 141 (1972).
(15) E. Lien, C. Hansch, and S. M. Anderson, *J. Med. Chem.*, **11**, 430 (1968).

Syntheses and Uncoupling Activities of Alkyl Dithiocarbazates and Alkyl Pyridinecarbonyldithiocarbazates

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A series of alkyl dithiocarbazates, alkyl 3-picolinoyldithiocarbazates, alkyl 3-nicotinoyldithiocarbazates, alkyl 3-isonicotinoyldithiocarbazates, and alkyl 3-picolinoyl-2-methyldithiocarbazates was prepared. These alkyl pyridinecarbonyldithiocarbazates were shown to be uncouplers of oxidative phosphorylation in mitochondria. The finding that uncoupling activity increased with increase in the length of the alkyl chains of the compounds indicates that hydrophobicity influences the activity. The nonyl derivatives had the highest activity. The results also suggested that a dissociable acidic proton is necessary for the uncoupling activity.

Various biologically active substances, such as antibacterial, antifungal, and nonsteroidal antiinflammatory agents, are known to be inhibitors or uncouplers of oxidative phosphorylation in mitochondria.[1] Thus in vitro experiments on the effects of various compounds on mitochondrial function may be a good way to find new series of biologically active reagents,[1c] although it is still uncertain whether mitochondria are directly involved in the site of action of these reagents. Recently, Bäuerlein and Keihl reported that nonylthiourea and nonylthiouracil effectively released the respiration of mitochondria.[2]

The alkyl 3-picolinoyldithiocarbazates reported previously,[3] **8–14**, have the same thiocarbamoyl structure as that in thiourea and thiouracil. Thus our recent finding (unpublished data) that they showed uncoupling activity prompted us to examine the effects of the complete series of alkyl dithiocarbazates **1–7** and alkyl pyridinecarbonyldithiocarbazates **8–34** on oxidative phosphorylation in mitochondria. Most uncouplers have a dissociable proton and an important role of this proton in the uncoupling has been stressed extensively.[4] Since the NH proton adjacent to the C=S group of the dithiocarbazates is expected to be dissociable, we synthesized the N^2-methylated alkyl 3-picolinoyldithiocarbazates **35–39** in order to examine the role of the acidic proton in the uncoupling action of this series of uncoupler.

Chemistry. Methyl[5] and ethyl dithiocarbazate[6] are already known. Attempts to prepare higher esters than *n*-propyl esters were reported to be unsuccessful,[7] but we obtained the higher esters **1–7** from *n*-propyl to *n*-nonyl ester in good yields by treating aqueous ethanolic solutions of the hydrazinium dithiocarbazates with alkyl iodides at room temperature and extracting the products with benzene (Scheme I).

The syntheses of methyl and ethyl pyridinecarbonyldithiocarbazates **8**, **9**, **17**, **18**, **26**, and **27** by reaction of potassium dithiocarbazates with alkyl iodides have been reported previously.[3,8] However, higher alkyl esters than propyl pyridinecarbonyldithiocarbazates could not be obtained by the procedure used for syntheses of the methyl and ethyl esters. Previously, we obtained alkyl 3-picolinoyldithiocarbazates **10–14** by adding alkyl iodides to a mixture of acid hydrazides, carbon disulfide, and potassium hydroxide in ethanol.[3]

In the present study, compounds **8–34** were prepared by the latter procedure. Reinvestigation of the latter procedure revealed that, even using an equimolar amount of alkyl iodide, large amounts of the *S,S'*-dialkyl derivatives were formed in addition to the desired *S*-alkyl derivatives **8–34**. Although *S,S'*-dimethyldithiocarbonate picolinoylhydrazone and *S,S'*-dimethyldithiocarbonate isonicotinoylhydrazone were obtained as crystals, the other *S,S'*-dialkyl derivatives were isolated as oily products that could not be obtained in analytically pure form. Five alkyl

Scheme I

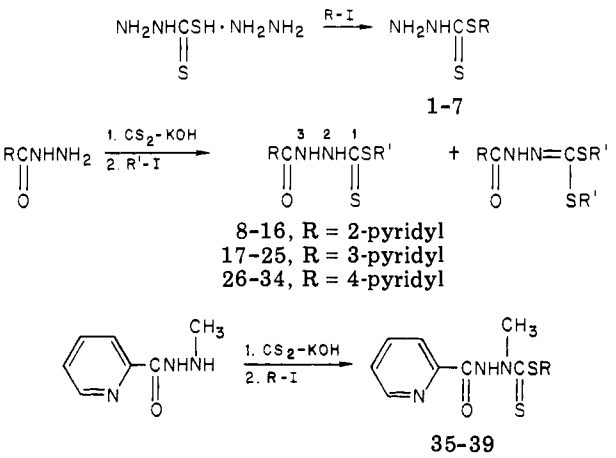

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Table I. Alkyl Dithiocarbazates

NH_2NHCSR (S)

Compd no.	R	Yield, %	Mp, °C	Formula[a]	100% uncoupling act.,[b] μM
1	n-C_3H_7	64	43-45	$C_4H_{10}N_2S_2$	–
2	n-C_4H_9	42	44-45	$C_5H_{12}N_2S_2$	–
3	n-C_5H_{11}	65	62-63	$C_6H_{14}N_2S_2$	900[c]
4	n-C_6H_{13}	57	53-55	$C_7H_{16}N_2S_2$	350[c]
5	n-C_7H_{15}	69	71-73	$C_8H_{18}N_2S_2$	140[c]
6	n-C_8H_{17}	66	62-63	$C_9H_{20}N_2S_2$	–
7	n-C_9H_{19}	63	78-80	$C_{10}H_{22}N_2S_2$	–

[a] All compounds were analyzed for C, H, and N. [b] A dash (–) means that activity was not tested. [c] Mitochondrial concentration: 2.12 mg of protein/3.3 mL.

Table II. Alkyl Pyridinecarbonyldithiocarbazates

$R_1CNHNCSR_3$ (R_2 on N; O on C; S on C)

Compd no.	R_1	R_2	R_3	Yield, %	Mp, °C	Formula[a]	100% uncoupling act., μM
8	2-Pyridyl	H	CH_3	29	154-155[b]	$C_8H_9ON_3S_2$	1870[c]
9	2-Pyridyl	H	C_2H_5	22	148-149[d]	$C_9H_{11}ON_3S_2$	1280[c]
10	2-Pyridyl	H	n-C_3H_7	24	134-135[e]	$C_{10}H_{13}ON_3S_2$	290[f]
11	2-Pyridyl	H	n-C_4H_9	20	136-137[g]	$C_{11}H_{15}ON_3S_2$	240[f]
12	2-Pyridyl	H	n-C_5H_{11}	21	121-122[h]	$C_{12}H_{17}ON_3S_2$	90[f]
13	2-Pyridyl	H	n-C_6H_{13}	24	115-116[i]	$C_{13}H_{19}ON_3S_2$	50[f]
14	2-Pyridyl	H	n-C_7H_{15}	15	102-103[j]	$C_{14}H_{21}ON_3S_2$	4.7[k]
15	2-Pyridyl	H	n-C_8H_{17}	28	106-107	$C_{15}H_{23}ON_3S_2$	3.7[k]
16	2-Pyridyl	H	n-C_9H_{19}	13	104-105	$C_{16}H_{25}ON_3S_2$	2.9[k]
17	3-Pyridyl	H	CH_3	32	159-160[l]	$C_8H_9ON_3S_2$	2160[c]
18	3-Pyridyl	H	C_2H_5	51	161-162[m]	$C_9H_{11}ON_3S_2$	1000[c]
19	3-Pyridyl	H	n-C_3H_7	16	156-157	$C_{10}H_{13}ON_3S_2$	370[c]
20	3-Pyridyl	H	n-C_4H_9	20	143-144	$C_{11}H_{15}ON_3S_2$	360[n]
21	3-Pyridyl	H	n-C_5H_{11}	22	145-146	$C_{12}H_{17}ON_3S_2$	105[n]
22	3-Pyridyl	H	n-C_6H_{13}	21	146-147	$C_{13}H_{19}ON_3S_2$	89[o]
23	3-Pyridyl	H	n-C_7H_{15}	15	145-146	$C_{14}H_{21}ON_3S_2$	14[o]
24	3-Pyridyl	H	n-C_8H_{17}	18	143-144	$C_{15}H_{23}ON_3S_2$	1.3[o]
25	3-Pyridyl	H	n-C_9H_{19}	9	144-145	$C_{16}H_{25}ON_3S_2$	1.1[o]
26	4-Pyridyl	H	CH_3	32	183-184[p] dec	$C_8H_9ON_3S_2$	1900[c]
27	4-Pyridyl	H	C_2H_5	10	166-167[q] dec	$C_9H_{11}ON_3S_2$	1200[c]
28	4-Pyridyl	H	n-C_3H_7	22	153-154 dec	$C_{10}H_{13}ON_3S_2$	109[r]
29	4-Pyridyl	H	n-C_4H_9	20	107-108 dec	$C_{11}H_{15}ON_3S_2$	62.5[r]
30	4-Pyridyl	H	n-C_5H_{11}	14	96-97 dec	$C_{12}H_{17}ON_3S_2$	17.5[r]
31	4-Pyridyl	H	n-C_6H_{13}	23	90-91 dec	$C_{13}H_{19}ON_3S_2$	6.58[s]
32	4-Pyridyl	H	n-C_7H_{15}	19	102-103 dec	$C_{14}H_{21}ON_3S_2$	1.95[s]
33	4-Pyridyl	H	n-C_8H_{17}	20	97-98 dec	$C_{15}H_{23}ON_3S_2$	0.84[s]
34	4-Pyridyl	H	n-C_9H_{19}	22	98-100 dec	$C_{16}H_{25}ON_3S_2$	0.86[s]
35	2-Pyridyl	CH_3	n-C_5H_{11}	32	86-87	$C_{13}H_{19}ON_3S_2$	Inactive[t]
36	2-Pyridyl	CH_3	n-C_6H_{13}	34	95-96	$C_{14}H_{21}ON_3S_2$	Inactive[t]
37	2-Pyridyl	CH_3	n-C_7H_{15}	29	68-69	$C_{15}H_{23}ON_3S_2$	Inactive[t]
38	2-Pyridyl	CH_3	n-C_8H_{17}	29	65-66	$C_{16}H_{25}ON_3S_2$	Inactive[t]
39	2-Pyridyl	CH_3	n-C_9H_{19}	34	64-65	$C_{17}H_{27}ON_3S_2$	Inactive[t]

[a] All compounds were analyzed for C, H, and N. [b] Lit.[3] mp 149-150 °C. [c] Mitochondrial concentration: 3.0 mg of protein/5.0 mL. [d] Lit.[3] mp 148-149 °C. [e] Lit.[3] mp 126-128 °C. [f] Mitochondrial concentration: 2.23 mg of protein/3.3 mL. [g] Lit.[3] mp 129-131 °C. [h] Lit.[3] mp 119-120 °C. [i] Lit.[3] mp 105-108 °C. [j] Lit.[3] mp 96-98 °C. [k] Mitochondrial concentration: 1.40 mg of protein/3.3 mL. [l] Lit.[3] mp 163-164 °C. [m] Lit.[3] mp 173-174 °C. [n] Mitochondrial concentration: 1.46 mg of protein/3.3 mL. [o] Mitochondrial concentration: 1.85 mg of protein/3.3 mL. [p] Lit.[8] mp 193-194 °C dec. [q] Lit.[8] mp 174-175 °C dec. [r] Mitochondrial concentration: 1.33 mg of protein/3.3 mL. [s] Mitochondrial concentration: 1.51 mg of protein/3.3 mL. [t] No effect up to about 500μM for 35 and up to about 100 μM for 36-39.

3-picolinoyl-2-methyldithiocarbazates **35–39** were prepared from 1-picolinoyl-2-methylhydrazine[9] by a method similar to that used to obtain compounds **8–34**.

The melting points and yields of the alkyl dithiocarbazates **1–7** and alkyl pyridinecarbonyldithiocarbazates **8–39** are given in Tables I and II, respectively.

Uncoupling Activities. Uncoupling activity was determined by measuring changes in state 4 respiration of rat liver mitochondria stimulated by alkyl pyridinecarbonyldithiocarbazates.[10] The compounds in each series stimulated state 4 respiration with succinate as substrate, and the uncoupling activity increased with the length of the alkyl chain, the derivatives with a nonyl group having the highest activities. These findings indicate that the hydrophobicity of the compounds greatly influences their uncoupling activity.

The N^2-methylated derivatives **35–39** of alkyl 3-picolinoyldithiocarbazates did not exhibit any significant uncoupling activity, suggesting that the presence of a dissociable proton is essential for the activity. The 3-isonicotinoyl derivatives **26–34** were consistently more potent than the 3-picolinoyl (**8–16**) and 3-nicotinoyl (**17–25**) derivatives with the same alkyl chain. Replacement of the acyl group of alkyl pyridinecarbonyldithiocarbazates by

Table III. Effect of Nonyl Pyridinecarbonyldithiocarbazates on State 4 Respiration of Mitochondria with Various Substrates[a]

RCNHNHCSC$_9$H$_{19}$ (O, S)

Compd no.	R	Concn, μM	Respiration rate (natoms of O/min) Glutamate + malate[b]	Succinate[c]	Ascorbate + TMPD[d]
16	2-Pyridyl	0	50	67	186
		1.0	89	167	220
		2.0	111	250	–
		5.0	180	–	–
		6.0	–	–	248
25	3-Pyridyl	0	64	75	173
		1.0	125	250	208
		2.0	178	300	227
		5.0	263	–	236
34	4-Pyridyl	0	46	83	165
		1.0	178	361	214
		2.0	278	–	222
		5.0	–	–	250

[a] The respiration rate of rat liver mitochondria was measured with a Clark type electrode at 25 °C. The mitochondria were suspended at 3.0 mg of protein in a medium containing 200 mM sucrose, 10 mM potassium phosphate, 2 mM $MgCl_2$, and 1 mM EDTA at pH 7.4. The total volume was 5.0 mL. [b] Glutamate (10 mM) plus 10 mM malate was used as substrate. [c] Succinate (10 mM) with 1 μg of rotenone was used as substrate. [d] Ascorbate (10 mM) plus 200 μM TMPD (*N,N,N',N'*-tetramethyl-*p*-phenylenediamine) with 2 μg of rotenone was used as substrate.

hydrogen caused marked decrease in the activity (Table I), suggesting that the electron-withdrawing ability of the pyridinecarbonyl group is also important for the uncoupling activity.

The nonyl derivatives (**16**, **25**, and **34**) of pyridinecarbonyldithiocarbazates in each series stimulated state 4 respiration when glutamate plus malate, or ascorbate plus TMPD (*N,N,N',N'*-tetramethyl-*p*-phenylenediamine), was used as substrate in the same way as they did with succinate as substrate (Table III). Furthermore, at concentrations of about 3 μM these compounds all released oligomycin-inhibited respiration almost completely with glutamate plus malate, or succinate, as substrate. Bäuerlein and Keihl[2] reported that nonylthiouracil and nonylthiourea stimulated state 4 respiration with succinate, but these compounds inhibited the transition from state 4 to state 3 with glutamate plus malate. Although pyridinecarbonyldithiocarbazates are similar to thiouracil and thiourea derivatives in thiocarbamoyl structure, their mechanism of action is probably different.

Experimental Section

Uncoupling Activity. Rat liver mitochondria were isolated by the method of Hogeboom[11] as described by Myers and Slater.[12] The protein concentration of mitochondria was determined by the Biuret method.[13] For determination of the uncoupling activity of a test compound, a suspension of state 4 mitochondria with succinate as substrate was titrated with a solution of the compound in Me_2SO. The respiration was stimulated almost linearly over the low concentration ranges of the compounds, but on further addition of the compounds the respiration rate gradually reached maximum rate. The minimum concentration causing maximal release of respiration was taken as the 100% uncoupling activity.[14] The activities listed in Tables I and II are means of values in at least three runs. Respiration was measured as oxygen uptake by mitochondria with a Galvani electrode, as described by Utsumi et al.,[15] using medium of pH 7.2, containing 200 mM sucrose, 10 mM phosphate, 2 mM $MgCl_2$, 1 mM EDTA, and 10 mM succinate. Rotenone (1 μg) was present in the reaction medium and the total volume of a reaction mixture was 3.3 mL, unless otherwise noted.

Syntheses. All melting points were determined by the capillary method and were uncorrected. NMR spectra were recorded with a JEOL PS-100 spectrometer using tetramethylsilane as an internal standard.

Alkyl Dithiocarbazates 1–7. The corresponding alkyl iodide (0.11 mol) in EtOH (40 mL) was added to a solution of hydrazinium dithiocarbazate (0.01 mol) in H_2O (40 mL). The mixture was stirred at room temperature overnight and then extracted three times with benzene (100 mL). The benzene layer was washed with H_2O, dried over Na_2SO_4, and evaporated in vacuo at below 60 °C. The residue was collected and washed well with cyclohexane to give colorless crystals.

Alkyl Pyridinecarbonyldithiocarbazates 8–34. Compounds **9–34** were prepared by a method similar to that described below for methyl 3-picolinoyldithiocarbazate (**8**).

Methyl 3-Picolinoyldithiocarbazate (8). Carbon disulfide (2.28 g, 0.03 mol) was added with stirring to a solution of picolinic acid hydrazide (2.74 g, 0.02 mol) in EtOH (10 mL) and KOH (1.12 g, 0.02 mol) in H_2O (2 mL), and the reaction mixture was stirred at room temperature for 30 min. Methyl iodide (2.84 g, 0.02 mol) in EtOH (3 mL) was added dropwise with cooling and then the mixture was stirred at room temperature overnight. The precipitate which formed was collected by filtration and recrystallized from isopropyl ether–$CHCl_3$ as colorless needles of **8** (1.31 g): mp 154–155 °C; NMR ($CDCl_3$) δ 2.67 (s, 3 H, SCH_3).

The filtrate was diluted with H_2O (20 mL) and extracted with $CHCl_3$ (20 mL). The $CHCl_3$ layer was dried over Na_2SO_4 and evaporated, and the residual oil was chromatographed on silica gel using benzene–$CHCl_3$ as eluent. Evaporation of the solvent from the first fraction gave a solid, which was recrystallized from isopropyl ether as colorless crystals of *S,S'*-dimethyldithiocarbonate picolinoylhydrazine (1.32 g): mp 107–108 °C; NMR ($CDCl_3$) δ 2.57, 2.59 [each s, each 3 H, $=C(SCH_3)_2$]. Anal. ($C_9H_{11}N_3OS_2$) C, H, N.

In the syntheses of compounds **12–16**, **20–25**, and **27–34**, the desired products did not precipitate from the reaction mixtures, and so the mixtures were diluted with H_2O and extracted with $CHCl_3$. Evaporation of the solvent from the $CHCl_3$ layer gave an oily product, which was chromatographed on silica gel using $CHCl_3$–benzene as eluent to give two fractions. The desired *S*-alkyl derivative obtained from the second fraction was recrystallized from isopropyl ether.

S,S'-Dimethyldithiocarbonate isonicotinoylhydrazone was obtained as crystals, but other *S,S'*-dialkyl derivatives were obtained as oily products. *S,S'*-Dimethyldithiocarbonate isonicotinoylhydrazone: mp 101–102 °C; NMR ($CDCl_3$) δ 2.56 [s, 6 H, $=C(SCH_3)_2$]. Anal. ($C_9H_{11}N_3OS_2$) C, H, N.

Alkyl 3-Picolinoyl-2-methyldithiocarbazates 35–39. Carbon disulfide (0.015 mol) was added with stirring to a solution of 1-picolinoyl-2-methylhydrazine[9] (0.01 mol) in ethanolic potassium hydroxide (0.56 g, 5 mL), and the mixture was stirred at room temperature for 30 min. The corresponding alkyl iodide (0.01 mol) was added. The mixture was stirred overnight and then filtered to remove the small amount of precipitate formed, and H_2O (20 mL) was added to the filtrate to give an oily product, which solidified on cooling. The solid was collected by filtration

and recrystallized from isopropyl ether as colorless needles.

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References and Notes

(1) (a) S. Muraoka and H. Terada, *Biochim. Biophys. Acta*, **275**, 271 (1972); (b) H. Terada, S. Muraoka, and T. Fujita, *J. Med. Chem.*, **17**, 330 (1974); (c) R. L. Williamson and R. L. Metcalf, *Science*, **158**, 1694 (1967); (d) M. W. Whitehouse, *Biochem. Pharmacol.*, **16**, 753 (1967).
(2) E. Bäuerlein and R. Keihl, *FEBS Lett.*, **61**, 68 (1976).
(3) S. Kubota, T. Okitsu, and Y. Koida, *Yakugaku Zasshi*, **90**, 841 (1970).
(4) W. G. Hanstein, *Biochim. Biophys. Acta*, **456**, 129 (1976).
(5) M. Busch and M. Starke, *J. Prakt. Chem.*, **93** (2), 49 (1916).
(6) J. Sandström, *Ark. Kemi.*, 4, 297 (1952); *Chem. Abstr.*, **47**, 9271*d* (1953).
(7) A. Toyoshima, K. Shimada, K. Sugiyama, and Y. Kawabe, *Yakugaku Zasshi*, **84**, 192 (1964).
(8) S. Yoshida and M. Asai, *Yakugaku Zasshi*, **74**, 951 (1954).
(9) S. Kubota, M. Uda, and M. Ohtsuka, *Chem. Pharm. Bull.*, **19**, 2331 (1971).
(10) Compounds possessing uncoupling activity released state 4 respiration and activated ATPase activity, but they did not inhibit state 3 respiration of mitochondria.
(11) G. H. Hogeboom, *Methods Enzymol.*, **1**, 16 (1955).
(12) D. K. Myers and E. C. Slater, *Biochem. J.*, **67**, 558 (1957).
(13) A. G. Gornall, C. J. Bardawill, and M. M. David, *J. Biol. Chem.*, **177**, 751 (1949).
(14) H. Terada and K. van Dam, *Biochim. Biophys. Acta*, **387**, 507 (1975).
(15) K. Utsumi, K. Kurahashi, M. Miyahara, and M. Yasude, *Cell Struct. Funct.*, **2**, 41 (1977).

Book Reviews

Drugs and Central Synaptic Transmission. Edited by P. B. Bradley and B. N. Dhawan. University Park Press, Baltimore, London, and Tokyo. 1976. xiv + 391 pp. 16 × 24 cm. $49.50.

This text is a collection of papers presented at a symposium in Oct 1974, at the Central Drug Research Institute in Lucknow, India, entitled, "Use of Pharmacological Agents in the Elucidation of Central Synaptic Transmission". The book contains material covering a broad spectrum of information on central neurotransmitter systems and is a compilation of three reviews and 33 research articles.

The text begins with two excellent reviews, viz., microelectrophoretic principles and practice by D. R. Curtis and a discussion by E. Costa et al. on basic principles of mass fragmentography, steady-state kinetics, and neurotransmitter system dynamics. Both of these chapters present, in detail, the general concepts, and importance, of recent advances in methodology. D. R. Curtis discusses the use of pharmacological agents in microelectrophoretic investigations for elucidating specific mechanisms in the process of neurotransmission at discrete neuronal sites. In addition, the chapter presents both the technical advantages and disadvantages associated with these studies. Costa and his colleagues stress the importance of turnover dynamics in Chapter 2 on multiple ion detection studies of steady-state kinetics and neurotransmitter system dynamics. The basic principles of mass fragmentography are presented as well as data on neurotransmitter interactions, viz., cholinergic–noradrenergic, cholinergic–serotonergic, and cholinergic–dopaminergic relationships, in specific nuclei of the brain.

A review of the effects of drugs on monoamines in the central nervous system is presented by N. E. Anden in Chapter 3. This short but concise summary details dopaminergic mechanisms in the corpus striatum and limbic system and describes the serotonergic and noradrenergic processes in the spinal cord.

These three review chapters are well presented and are worthwhile reading for neuroscientists. The remaining 33 chapters deal with various topics without any logical sequence of presentation. This compilation basically includes recent laboratory findings and the chapters are written as basic journal research reports, including a short introduction, methods, results, and a discussion. The topics covered basically stress the use of drugs as tools for elucidating basic mechanisms. Practically all aspects of central neurotransmission are presented, including pharmacological, anatomical, physiological, biochemical, and behavioral information.

The title of the book, i.e., "Drugs and Central Synaptic Transmission", may be somewhat misleading, for the text is more accurately described by the title of the symposium. The book is not a general treatise on pharmacological aspects of central neurotransmission and perhaps was not meant to be. Specific chapters in the book may be useful as a reference to those involved in that particular area of research.

Vanderbilt University School of Medicine **Lynn Wecker**

Biological Aspects of Inorganic Chemistry. Edited by A. W. Addison, W. R. Cullen, D. Dolphin, and B. R. Jones. Wiley-Interscience, New York, N.Y. 1977. vii + 410 pp. 15.5 × 23.5 cm. $22.00.

This book presents the invited papers of a 1976 Symposium on the title subject. The program choices were well considered, so the book represents an interesting overview of some current topics in inorganic biochemistry. As with many published symposia the nature of the subject matter and the level of the presentations vary widely. Particularly noteworthy to the reviewer were Buckingham's chapter on hydrolases and Gray's article on protein electron-transfer mechanisms. Other topics include oxidative phosphorylation (Wang), zinc biochemistry (Vallee), iron–sulfur proteins (Holm), ionophores (Dunitz), B_{12} (Abeles), environmental aspects (Wood et al.), heme redox proteins (Williams), and two conspicuously abiological treatments of N_2 fixation (Shilov, Chatt). Proofing is unfortunately sparse. Gray's otherwise superb chapter is marred by a number of serious typographical errors (e.g., omission of exponential terms in equations).

It is disappointing that some mechanism was not provided for including some poster session material, as this material is often referred to in the main text.

Despite these minor criticisms, the overall quality of the volume is sufficiently high to justify its moderate price. It will serve as a valuable reference not only for specialists but also for those seeking an overview of some recent topics of bioinorganic interest.

University of Rochester **George McLendon**

Methods of Development of New Anticancer Drugs. USA–USSR Monograph. Edited by Joseph F. Saunders and Stephen K. Carter. National Cancer Institute Monograph No. 45. U.S. Government Printing Office, Washington, D.C. 1977. 262 pp. 22 × 28.5 cm. $9.50.

This monograph evolved from the USA–USSR Cooperative Agreement of 1972. The publication is for sale *only* by the