Synthesis of 6-Substituted β-Carbolines That Behave as Benzodiazepine Receptor Antagonists or Inverse Agonists

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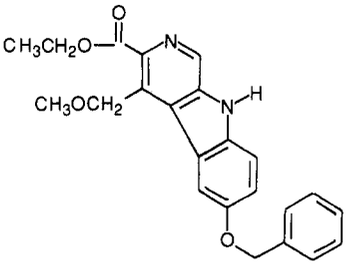
The synthesis of the first β-carboline, 6-(benzylamino)-β-carboline (**1c**), to be devoid of a substituent at the 3-position and that still binds to benzodiazepine receptors with potent affinity is described. Furthermore, **1c** proved to be a partial inverse agonist when tested in mice. Addition of the benzylamino group at the 6-position of the β-carboline nucleus is primarily responsible for the activity of β-carbolines **1b** and **1c**. The importance of the N_b-nitrogen atom for binding affinity was also demonstrated since 3-(benzylamino)carbazole (**6**) exhibited little or no affinity for benzodiazepine receptors in vitro, in contrast to the activity of **1c**.

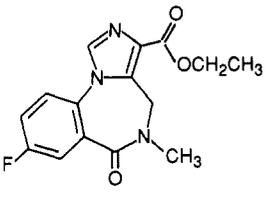
Several β-carboline-3-carboxylates have been shown to bind with high affinities to benzodiazepine receptors in the central nervous system. Initially, these compounds were shown to antagonize the principle pharmacologic actions of the benzodiazepines.[1] In addition, many of these compounds have subsequently been shown to possess "intrinsic" pharmacologic actions that are opposite to those of the benzodiazepines. Such compounds have been termed benzodiazepine receptor inverse agonists.[2] For example, 3-(ethoxycarbonyl)-β-carboline, BCCE, and the 3-[(methylamino)carbonyl]-β-carboline FG 7142 have been shown to produce a syndrome resembling stress or anxiety in rodents and primates, including humans.[3-6] In addition, 3-(methoxycarbonyl)-β-carboline, BCCM, and 6,7-dimethoxy-4-ethyl-3-(methoxycarbonyl)-β-carboline, DMCM, have been shown to be potent convulsants.[7-9] The term inverse agonist has been used to distinguish this group of compounds from benzodiazepine antagonists such as Ro 15-1788. The latter compound binds to benzodiazepine receptors (Bz R) with high affinity and can antagonize the actions of either agonists or inverse agonists, but does not elicit pharmacologic actions of its own.[10] It has been shown that substitution at the 5- or 6-position of the β-carboline-3-carboxylates can affect the pharmacological profile. For example, 6-(benzyloxy)-4-(methoxymethyl)-3-(ethoxycarbonyl)-β-carboline, ZK-93423, differs significantly in its in vivo activity from BCCM or DMCM in that it is very similar to that of the agonist diazepam.[11]

Recently the synthesis of a number of 3,6-disubstituted β-carbolines that demonstrated high affinity for the benzodiazepine receptor was completed.[12] We report that one of these compounds, 6-(benzylamino)-3-(methoxycarbonyl)-β-carboline, **1a**, exhibits a biological profile in mice that resembles Ro 15-1788, since **1a** blocks the anticonvulsant actions of diazepam, but does not possess proconvulsant actions. Thus, by simply substituting a benzylamino group, an isoster for the benzyloxy portion of ZK-93423, for hydrogen at position 6 of BCCM, the convulsant and proconvulsant activity of BCCM has been completely eliminated.

The activity of **1a** coupled with the activity of a structurally related compound, 7,12-dihydropyrido[3,2-*b*:5,4-*b*']diindole, **2**, a rigid, diazepam antagonist that is devoid of an ester function,[13] prompted the formulation of a model for the binding of ligands to Bz R.[14] In agreement with this model, two β-carbolines, 6-(benzylamino)-3-(hydroxymethyl)-β-carboline and 6-(benzylamino)-β-carboline, **1b** and **1c**, respectively, were prepared. Both of these mole-



ZK-93423



Ro 15-1788

†National Institute of Diabetes and Digestive and Kidney Diseases.

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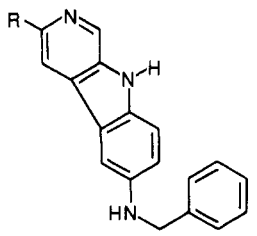
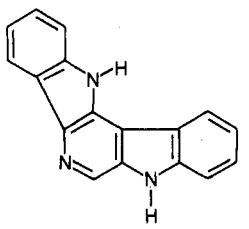
Scheme I. In Vitro Binding (IC_{50}) of β-Carboline Derivatives





1a, R = CO_2CH_3 (10 nM)
1b, R = CH_2OH (76 nM)
1c, R = H (106 nM)

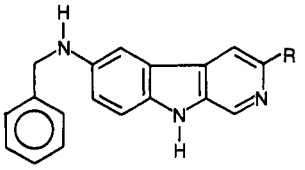
2, (5 nM)

cules are devoid of an ester function at the 3-position; however, both were found to possess high affinity for Bz R. The relative affinities of **1b** (IC_{50} = 76 nM) and **1c** (IC_{50} = 106 nM) are 1 order of magnitude greater than that of the 3-substituted β-carboline 3-(hydroxymethyl)-β-carboline, **3** (3HMC, IC_{50} = 1470 nM),[15] and the unsubstituted derivative β-carboline **4** (norharmane, IC_{50} = 1670 nM) (Scheme I). The affinities of **1b** and **1c** are comparable, therefore, to the antagonist 3-acetyl-β-carboline (IC_{50} = 58 nM)[15] and to esters such as cyclopentyl-β-carboline-3-carboxylate (IC_{50} = 50 nM).[12]

Chemistry. The 6-amino-3-(methoxycarbonyl)-β-carboline, prepared as previously reported,[12] was reacted with 1.1 equiv of benzaldehyde, followed by the addition of sodium cyanoborohydride.[16] This process provided the 6-benzylamino analogue **1a** in excellent yield. This material was then treated with $LiBH_4$ to provide 6-(benzylamino)-3-(hydroxymethyl)-β-carboline, **1b**, under analogous conditions to those previously reported for synthesis of 3HMC (**3**).[15] β-Carboline **4** was prepared by oxidative decarboxylation (SeO_2, HOAc) of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid and was subsequently transformed into 6-nitro-β-carboline.[17] Reduction of 6-nitro-β-carboline to provide 6-amino-β-carboline, **5**, was effected by catalytic hydrogenation (Pd/C). The 6-amino derivative was converted into 6-(benzylamino)-β-carboline, **1c**, analogous to the procedure described above for preparation of **1a**. Similarly, carbazole was nitrated[18] and converted (H_2, Pd/C;[19] $NaCNBH_3$, PhCHO) into 3-(benzylamino)-carbazole, **6**, also according to the procedure detailed for **1a** (see the Experimental Section).

Pharmacology. The protocols employed for biological testing have been reported in detail in ref 15; adult, male mice (20–25 g) were used in the studies. To determine whether compounds **1a**, **1b**, or 1c were anticonvulsants, the agents were suspended and injected intraperitoneally (0.1 mL in 10% diluted emulphor–90% saline solution) 5 min prior to administration of pentylenetetrazole [PTZ, 80 mg/kg in saline, ip injection (0.1 mL)]. To assess whether these agents were proconvulsant, mice were injected (0.1 mL) with the drug and 5 min later challenged with a subconvulsant (40 mg/kg) dose of PTZ. Antagonist action was determined by pretreating animals with diazepam (0.1 mL, 2.5 mg/kg dissolved in 10% diluted emulphor–90% saline), followed 5 min later by injection of drug (volume,

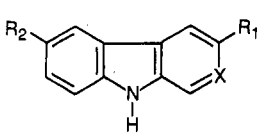
Table I. Biological Activity of β-Carbolines **1a–c**



Agent[a]	R	*in vitro*[b] IC_{50}, nM	Proconvulsant Actions ED_{50}, mg/kg[c]	Diazepam Antagonism ED_{50}, mg/kg[d]	Analyses[g]
1a	CO_2CH_3	10	—[e]	15.5	$C_{20}H_{17}N_3O_2 \cdot 1/4\ H_2O$
1b	CH_2OH	76	40	—[e]	$C_{19}H_{17}N_3O \cdot 0.8\ H_2O$
1c	H	106	28	38	$C_{18}H_{15}N_3 \cdot 2HCl \cdot 1\ 1/4\ H_2O$
3		1470			
4		1620[f]			$C_{11}H_8N_2$
5		1300nM[f]			$C_{11}H_9N_3 \cdot 1/4\ H_2O$
6		>5000nM[f,h]			$C_{19}H_{16}N_2 \cdot HCl \cdot 1/4\ H_2O$

[a] Administered as the HCl salts.
[b] See reference 15 for details.
[c] Dose necessary to induce convulsions in 50% of the mice which had been previously given a subconvulsant dose of ptz (40 mg/kg).
[d] Dose necessary to antagonize the anticonvulsant effects of diazepam (2.5 mg/kg) in mice which had been given a convulsant dose of ptz (80 mg/kg), see reference 15 for details.
[e] Did not elicit activity at the highest dose tested (40 mg/kg).
[f] Binding affinity was too low to warrent biological screening.
[g] Analyzed for C,H,N. Structures were determined by NMR (250 mHz), IR and mass spectroscopy.
[h] Only tested *in vitro* once because of the high IC_{50} value.

Scheme II



3, R_1 = CH_2OH, R_2 = H, X = N
4, R_1 = R_2 = H, X = N
5, R_1 = H, R_2 = NH_2, X = N
6, R_1 = H, R_2 = $NHCH_2Ph$, X = CH

0.1 mL) or vehicle, after which (5 min) a convulsant dose (CD_{100}) of PTZ (80 mg/kg) was administered. Animals were observed by two independent raters for the development of clonic–tonic convulsions. Animals were noted as "protected" if no seizures developed within 15 min; injections of PTZ (80 mg/kg) alone or with vehicle produced clonic–tonic seizures within 5 min.

None of the compounds tested (**1a**, **1b**, or **1c**) displayed anticonvulsant activity since PTZ (80 mg/kg) produced seizures in all animals even at the highest doses (40 mg/kg) tested. Interestingly **1a** did not possess proconvulsant activity at the highest dose (40 mg/kg) administered; however, this compound antagonized the anticonvulsant effects of diazepam with an ED_{50} of 15.5 mg/kg (see Table I). 6-(Benzylamino)-3-(hydroxymethyl)-β-carboline, **1b**, had proconvulsant activity with an ED_{50} of 40 mg/kg, but did not antagonize the anticonvulsant effects of diazepam under the conditions employed. This is noteworthy since 3HMC[15] at a dose of 25 mg/kg produced convulsions in 60% of the animals tested in the proconvulsant paradigm. Finally 6-(benzylamino)-β-carboline, **1c**, did behave as a proconvulsant (ED_{50} = 25 mg/kg) and also antagonized the anticonvulsant actions of diazepam with an ED_{50} of 28 mg/kg. It should be noted that the β-carboline harmaline is a tremorigen; however, this action is probably not mediated by Bz R.[8]

To examine further the interaction of β-carbolines with

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Bz R, 3-(benzylamino)carbazole, **6**, was prepared (Scheme II). This compound is devoid of the pyridinyl nitrogen atom in ring C of the β-carboline nucleus; **6** exhibited little or no affinity (I_{50} > 5000 nM) for Bz R. The lack of affinity of **6** illustrates the importance of electron density in ring C of the β-carboline derivatives **1b** and **1c** imparted by the pyridinyl nitrogen atom. Whether this effect is due to interaction of the receptor with the indole NH function and/or with the pyridine nitrogen is under investigation. Moreover, the lack of affinity of β-carboline **4** or 6-amino-β-carboline, **5**, for Bz R supports the importance of the lipophilic benzyl group at the 6-position of **1a–c** with respect to affinity of these ligands for Bz R.

Conclusion. Most investigations have demonstrated that substitution at the 3-position of a β-carboline with an ester function is necessary for high affinity binding to benzodiazepine receptors. This study is the first demonstration of a β-carboline that is devoid of a 3-substituent that binds to the Bz R with an $IC_{50} \leq 100$ nM. Since **1b** and **1c** are devoid of an ester function at position 3, these and related analogues will not be prone to degradation via esterase enzymes[20] and should be more amenable for studies in vivo. Moreover, substitution of the 6-benzylamino group, which serves as an isoster for the 6-benzoloxy group of ZK-93423, for hydrogen at position 6 of BCCM has altered its activity from a convulsant (BCCM) to **1a**, a compound that in a convulsant/anticonvulsant paradigm only blocks the actions of diazepam. In this respect **1a** resembles a benzodiazepine antagonist such as Ro 15-1788. Other pharmacologic paradigms have also been employed to discriminate Bz antagonists from Bz R inverse agonists.[3] A more complete examination of the pharmacological actions of **1a–c** will be necessary to better define the profiles of these 6-(benzylamino)-β-carbolines.

Experimental Section

Microanalyses were performed on a F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. NMR spectra were recorded on a Brucker 250-MHz NMR spectrometer. IR spectra were recorded on a Beckman Acculab-1 instrument, while low-resolution mass spectral data were determined on a Hewlett-Packard 5855 GC-mass spectrometer. High-resolution mass spectra were taken on a Finnigan HR mass spectrometer.

Analytical TLC plates used were E. Merck Brinkman UV-active silica gel or alumina on plastic. The preparation of 6-nitro-β-carboline,[17] 3-nitrocarbazole,[18] and 3-aminocarbazole[19] have been previously reported.

6-(Benzylamino)-3-(methoxycarbonyl)-β-carboline (1a). KOH pellets (431 mg, 7.7 mmol) were added in one portion to a stirred suspension of 6-amino-3-(methoxycarbonyl)-β-carboline dihydrochloride (2.0 g, 6.4 mmol) in dry CH_3OH (200 mL). To the resulting orange solution was added benzaldehyde (750 mg, 7.1 mmol) in CH_3OH (25 mL). After the mixture was stirred for 30 min, $NaCNBH_3$ (575 mg) was added and the solution that resulted was stirred for 18 h at room temperature. The solvent was concentrated (10 mL) under reduced pressure and HCl (2 N, 100 mL) was added. The acidic solution was stirred at 0 °C for 30 min, after which the pH was adjusted to 11 (10% KOH). The aqueous layer was extracted with $CHCl_3$ (4 × 200 mL). The organic extracts were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield **1a** (1.73 g, 82%): mp 206–207 °C (EtOAc/CH_3OH); IR (KBr) 3380, 3080, 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.87 (3 H, s), 4.37 (2 H, d, J = 6 Hz), 6.11 (1 H, t, J = 6 Hz, NH), 7.07 (1 H, dd, J_1 = 2 Hz, J_2 = 9 Hz), 7.18–7.46 (7 H, m), 8.70 (1 H, s), 8.81 (1 H, s), 11.62 (1 H, s, indole NH); MS (CI, CH_4), m/e 332 (M + 1). Anal. ($C_{20}H_{17}N_3O_2$·0.25H_2O) C, H, N (high-resolution MS m/e 331.1304 ($C_{20}H_{17}N_3O_2$ requires 331.1321)).

6-(Benzylamino)-3-(hydroxymethyl)-β-carboline (1b). To a solution of **1a** (1.0 g, 3.2 mmol) in dry THF (200 mL) was added $LiBH_4$ (1.0 g) and the mixture was stirred for 24 h. To this slurry were added ice (100 g) and HCl (2 N, 40 mL), and the reaction mixture was stirred for 5 h. The pH was then adjusted to 11 (10% KOH). The aqueous layer was extracted with $CHCl_3$ (5 × 200 mL), and the organic layers were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure, and CH_3OH (200 mL) was added to the residual solid. Hydrogen chloride gas was subsequently passed through the mixture until saturation. The volume was reduced (25 mL) and anhydrous ether (25 mL) added. The precipitate that resulted was filtered to yield **1b** (730 mg, 60.3%) as the hydrochloride salt: mp 271–273 °C; IR (KBr) 3340–3210, 1505 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.54 (2 H, s), 4.95 (2 H, s), 7.27–7.37 (4 H, m), 7.52 (2 H, d, J = 6.5 Hz), 7.64 (1 H, d, J = 9 Hz), 7.74 (1 H, d, J = 9 Hz), 8.16 (1 H, s, NH), 8.62 (1 H, s), 9.11 (1 H, s), 12.74 (1 H, s, indole NH); ^{13}C NMR (Me_2SO-d_6) δ 47.47, 64.50, 101.34, 110.64, 112.34, 117.85, 121.21, 126.50, 127.32, 127.96, 128.17, 132.15, 134.07, 135.25, 140.49, 142.55, 148.96; MS (CI, CH_4), m/e 304 (M + 1); high-resolution MS m/e 303.1365 ($C_{19}H_{17}N_3O$ requires 303.1372).

Compound **1b**·2HCl was converted into its free base **1b**: mp 220–221 °C. Anal. ($C_{19}H_{17}N_3O$·0.8 H_2O) C, H, N.

6-(Benzylamino)-β-carboline (1c). 6-Amino-β-carboline (**5**) and benzaldehyde were reacted under the analogous conditions employed for preparation of **1a** to provide **1c**. The free base **1c** was converted into the dihydrochloride salt by stirring in a saturated solution of CH_3OH (HCl (g)): mp 236–238 °C; IR (KBr) 3340–2960, 1620, 1500 cm^{-1}; ^1H NMR (D_2O, H_2O irradiated δ H_2O 4.75) δ 4.63 (2 H, s), 7.25–7.42 (5 H, m), 7.59 (1 H, dd, J_1 = 3 Hz, J_2 = 6 Hz), 7.78 (1 H, d, J = 9 Hz), 8.10 (1 H, d, J = 3 Hz), 8.37 (1 H, d, J = 7 Hz), 8.46 (1 H, d, J = 6 Hz), 9.30 (1 H, s); ^{13}C NMR (Me_2SO-d_6) δ 47.45, 101.26, 107.03, 109.39, 112.46, 114.59, 118.44, 120.94, 126.54, 127.42, 127.54, 128.18, 128.33, 132.72, 134.07, 135.71, 137.25, 141.24; MS (CI, CH_4), m/e 274 (M + 1). Anal. ($C_{18}H_{15}N_3$·2HCl·1.25H_2O) C, H, N.

β-Carboline (4). Selenium dioxide (20 g, 0.18 mol) was added to a suspension of 1,2,3,4-tetrahydro-β-carboline-3-carboxylate (20 g, 0.091 mol) in glacial acetic acid (500 mL). The reaction mixture was brought to reflux after which all solid material went into solution and the solution was held at reflux for 24 h. The mixture was vacuum filtered while hot, and the solvent was removed under reduced pressure to yield a red oil. Water (500 mL) was added to the oil and the pH adjusted to 10 (concentrated NH_4OH). The aqueous layer was extracted with EtOAc (3 × 400 mL). The EtOAc extracts were combined, extracted with 5% KCN (2 × 500 mL) and brine (1 × 500 mL), and dried (K_2CO_3). The solvent was removed under reduced pressure to yield a solid, which was recrystallized from EtOAc to yield **4** (9.6 g, 62%): mp 199–200 °C; IR (KBr) 3130–2880, 1430 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.23 (1 H, m), 7.56 (3 H, m), 8.09 (1 H, d, J = 5 Hz), 8.22 (1 H, d, J = 8 Hz), 8.33 (1 H, d, J = 5 Hz), 8.90 (1 H, s), 11.61 (1 H, s indole NH); MS (CI, CH_4), m/e 169 (M + 1). Anal. ($C_{11}H_8N_2$) C, H, N.

6-Amino-β-carboline Dihydrochloride (5). A suspension of 6-nitro-β-carboline (3.0 g, 14 mmol) and Pd/C (5%, 340 mg) in CH_3OH (500 mL) was placed under 1 atm of H_2 and stirred for 24 h. The reaction mixture was filtered after which anhydrous HCl(g) was passed through the solution for 10 min at 0 °C. The solvent volume was reduced to 25 mL and anhydrous ether was added (200 mL), and the precipitate that resulted was collected by vacuum filtration to yield **5** (2.91 g, 81%): mp >300 °C; IR (KBr) 3092–2803, 1506 cm^{-1}, MS (CI, CH_4), m/e 184 (M + 1). This salt was converted into the free base (mp 292–94 °C (lit.[17] mp 297–98.5 °C)), 6-amino-β-carboline, the spectral properties of which were identical with those reported in the literature.[17]

3-(Benzylamino)carbazole (6). To a solution of 3-aminocarbazole (890 mg, 4.9 mmol) in dry CH_3OH (150 mL) was added benzaldehyde (571 mg, 5.4 mmol). After the solution was allowed to stir for 20 min, $NaCNBH_3$ (1.0 g) and AcOH (5 drops) were added. The reaction mixture was permitted to stir for 48 h, after which the solvent was reduced (10 mL) and HCl was added (6 N, 100 mL) at 0 °C. After the mixture was stirred for 20 min at 0 °C, the pH was adjusted to 10 (concentrated NH_4OH) and the aqueous layer was extracted with EtOAc (3 × 150 mL). The

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EtOAc was removed under reduced pressure to yield an oil, which was purified by column chromatography (silica gel, 25% hexane–75% EtOAc) to yield **6** (410 mg, 30%): mp 160–165 °C. This compound was converted into its hydrochloride salt by stirring in a saturated solution of CH_3OH (HCl(g)) IR 3280–3120, 1430 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.55 (2 H, s), 6.81 (1 H, d, J = 7.5 Hz), 7.0 (1 H, t, J = 7.7 Hz), 7.11–7.64 (10 H, m), 8.05 (1 H, d, J = 7.8 Hz), 11.29 (1 H, s); MS (15 eV), m/e (relative intensity) 272 (100), 181 (59). Anal. ($C_{19}H_{17}N_2Cl$·0.25H_2O) C, H, N (high-resolution MS m/e 272.1316 ($C_{19}H_{16}N_2$ requires 272.1313)).

The potencies of **1a–c** as inhibitors of [^{3}H]diazepam binding to benzodiazepine receptors were determined as described[15] with minor modifications. In brief, cerebral cortex from adult, male Sprague–Dawley rats (Taconic Farms, Germantown, NY) was weighed and disrupted in 100 volumes of 50 mM Tris·HCl buffer (pH 7.4) with a Brinkmann Polytron (setting 6–7, 15 s). The tissue homogenization–centrifugation procedure was repeated two more times, and the final pellet resuspended in 50 volumes of Tris·HCl buffer. An aliquot (0.2 mL) of tissue suspension was added to 0.6 mL of assay buffer and 0.1 mL of varying concentrations of either **1a–c**, buffer, or flunitrazepam (final concentrations, 5 μM). Reactions were initiated by the addition of 0.1 mL of [^{3}H]diazepam (final concentration, 2 nM; sp act. 70 Ci/mmol) and terminated 90 min (4 °C) later by rapid filtration through Whatman GF/B filters and washing (two 5-mL aliquots of buffer) with a Brandel M-24R filtering manifold (Brandel Instruments, Gaithersburg, MD). Nonspecific binding, which was measured in the presence of 5 μM flunitrazepam, represented <5% of the total binding. Filters were air-dried and placed in scintillation vials containing 4 mL of Ready-Solv MP (Beckmann Instrument Co., Fullerton, CA), and radioactivity was measured with a Beckmann LS 5801 liquid scintillation spectrometer. The IC_{50} value (that concentration of compound inhibiting the specific binding of [^{3}H]diazepam by 50%) was estimated from a Hill plot[21] with six to eight concentrations of inhibitor. The IC_{50} values presented are $\bar{x}$ values obtained from three independent determinations with an SEM < 10%.

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Book Reviews

Metal Ions in Biological Systems. Volume 20. Concepts on Metal Ion Toxicity. Edited by H. Sigel. Marcel Dekker, Inc., New York. 1986. xxiv + 386 pp. 16 × 24 cm. ISBN 0-8247-7540-6. $85.00.

Metal ion toxicity is a major focus of concern in environmental and health-related fields particularly in this technological age where the term pollution has become a household word. Thus this treatise on "Concepts on Metal Ion Toxicity" is a handy source of information that covers areas of interest to scientists ranging from geologists to biologists to chemists. The topics are divided into areas progressing from distribution descriptions to biological analytical methods.

Chapters 1 (G. Sposito) and 2 (R. B. Martin) provide an excellent background to metal ion distribution and transport on and over Earth in the former, and specific metal ion chemical and physical properties in the latter. These two chapters, while easy to read, provide fascinating tidbits of insight to metal ion occurrence and behavior.

Aquatic systems are discussed in Chapters 3 (E. Eichenberger) and 4 (G. K. Pagenkopf), respectively. These two chapters are nicely interlinked. Eichenberger provides background into the double role of the metals and the fine line between essentiality and toxicity as well as mechanisms that influence the response within the aquatic community. In Chapter 4 Pagenkopf develops a quantitative chemical model based on the results of toxicity studies on fish, whereby toxicity is related to a variety of chemical factors such as hardness and pH.

Chapter 5 (F. T. Bingham, F. J. Peryea, and W. M. Jarrell) bring the subject back to "solid ground" with an agriculturally related discussion of the factors affecting metal uptake by plants that includes diagnosis and corrective measures. This chapter complements the aquatic chapters quite well and provides a smooth link to the animal kingdom, the subject of the remaining chapters.

The next chapters deal with metal ion toxicity in humans. Chapter 6 (P. B. Hammond and E. C. Foulkes) is a well-written overview of eight specific metals, which includes historical background as well as absorption, distribution, excretion, and toxicity data. In Chapter 7 (M. R. S. Fox and R. M. Jacobs) a short background on general vitamin–mineral nutrients is provided, followed by an in-depth treatment of two essential nutrients, selenium and zinc. Chapter 8 (A. Leonard) leads the foray into chromosomal aberrations induced by heavy metals. After an introduction to chromosomal changes with helpful illustrative photos is provided, the results of cytogenetic monitoring for a variety of metals are outlined and discussed. Chapter 9 (M. Costa and J. D. Heck) continues on the cellular level, discussing metal ion carcinogenesis. Cellular uptake and distribution of metal ions and the effect of metal ions on cell growth, DNA, and the production of tumors are discussed.

Chapters 10 (J. D. Heck and M. Costa) and 11 (H. G. Seiler) provide the analytical finale: detection of metal ions and toxicity. Chapter 10 treats in vitro analysis, including biochemical, microbiological, and mammalian cell culture methods. In Chapter 11 the specifics and problems of analysis for toxic trace elements in biological materials are treated.

This volume is exceptionally well arranged with respect to presentation of the different aspects of metal ion toxicity in a logical fashion, starting with the overview of distribution, progressing through aquatic, agricultural, and animal studies, to closing with current analytical techniques. Each chapter provides sufficient background for a reader outside of the area as well as the current state of knowledge, with recent references, including a number of 1985 citations. This volume provides fascinating insight to the dual role of metal ions, essentiality and toxicity, and is clearly a welcome addition to the series.

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Modern Analysis of Antibiotics. Edited by Adorjan Aszalos. Marcel Dekker, New York. 1986. xvi + 535 pp. 18 × 26 cm. ISBN 0-8247-7358-6. $89.75.

This text describes a wide range of chemical and biological procedures for analyzing antibiotics. These procedures have many applications such as in the search for new antibiotics, determination of mechanism of biological activity, and quantitation for quality control of manufactured products. The book does not