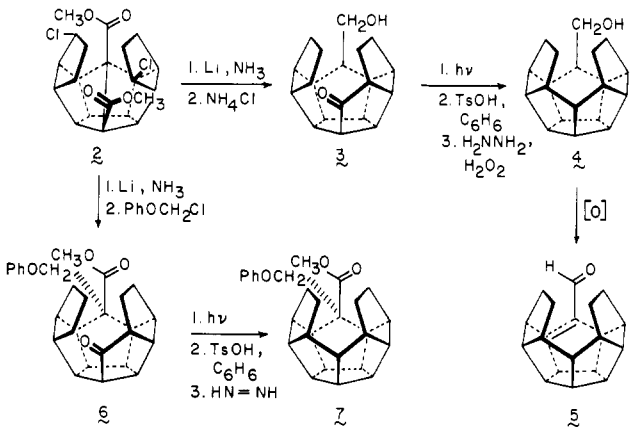
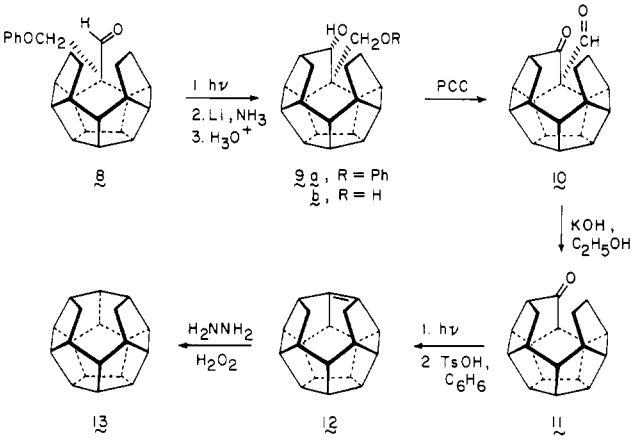
Scheme I



Scheme II



would effectively deter enolization of the carboxaldehyde functionality yet prove readily removable at a later stage. The selection of a pendant side chain had to be made judiciously since its role was necessarily multifaceted. Thus, its introduction must be achieved via S_N2 methodology, and it must survive those steps required for construction of two framework bonds on the opposite molecular surface as well as alteration of the carbomethoxy oxidation level. Most importantly, the R group in question must not foster added photodecarbonylation of the aldehyde nor engage in capture of this photoexcited carbonyl group.

Chloromethyl phenyl ether[8] satisfies all of these requirements. As indicated in the formulas, lithium–liquid ammonia reduction of **2** and immediate addition of 1 equiv of the electrophile gave **6** (48%). The phenoxymethyl side chain causes interference neither during the three-step conversion to **7** nor during the ensuing Dibal-H reduction and PCC oxidation of this triseco ester. With **8** (Scheme II) in hand, it was determined that the $PhOCH_2$– residue likewise does not become entangled with proximate functionality during photochemical cyclization to **9a** (36%). As always, the lowered yield observed in this step results from competitive photodecarbonylation.

Reduction of **9a** under Birch conditions delivered a dihydrobenzene product, aqueous acid hydrolysis of which furnished **9b** in 99% isolated yield. This diol undergoes efficient oxidation to β-keto aldehyde **10** upon treatment with pyridinium chlorochromate. This intermediate conforms to the susceptibility of this class of compounds to retroaldol cleavage in alkaline solution and provides diseco ketone **11** in 37% overall yield. The risk of complications due to enolization α to a carbonyl site was now behind us.

The conversion of **11** to **13** via **12** proved to be quite uneventful and satisfyingly efficient (65% overall). Upon being heated with H_2-presaturated 10% palladium on carbon at 250 °C for >4.5 h as described earlier,[4] **13** was transformed with 40–50% efficiency into dodecahedrane (**1**). The colorless crystalline hydrocarbon can be rountinely obtained in >98% purity after a *single* recrystallization of such product mixtures from benzene.

As fully expected, the ^1H and ^{13}C NMR spectra of **1** (in $CDCl_3$) are characterized by singlets, the former at δ 3.38 and the latter at 66.93 ppm. The ^{13}C–H coupling constant of 134.9 Hz is somewhat larger than the value earlier calculated by Mislow (128.1 Hz),[9] but entirely comparable to those of the dimethyl derivative (131.2, 135.0 Hz).[5] The vibrational frequencies exhibited by this I_h symmetric molecule (120 identity operations) agree fully with a highly rigid network of interlinked methine units. Three infrared-active bands are observed at 2945, 1298, and 728 cm^{-1}; its eight Raman-active frequencies occur at 2954, 2938, 1324, 1164, 1092, 840, 676, and 480 cm^{-1}.[10] In general, these findings compare reasonably well with values calculated by Ermer.[11] The hydrocarbon gives no visible evidence of melting at temperatures up to 450 °C.

In summary, the total synthesis of dodecahedrane has been achieved in 23 steps from cyclopentadienide anion. While this already brief sequence is certain to see improvement in the future, quantities of this most exquisite of polycondensed ring systems are now available for further experimentation. In ongoing research, we intend to address some of the many questions relating to its possibly distinctive physical and chemical properties.[12]

Registry No. 1, 4493-23-6; **2**, 71342-50-2; **6**, 82390-75-8; **7**, 82390-76-9; **8**, 82390-77-0; **9a**, 82390-78-1; **9b**, 82390-79-2; **10**, 82390-80-5; **11**, 82390-81-6; **12**, 82390-82-7; **13**, 82390-83-8; chloromethyl phenyl ether, 6707-01-3.

(8) Barber, H. J.; Fuller, R. F.; Grea, M. B.; Zwartouw, H. T. *J. Appl. Chem.* **1953**, *3*, 266.

(9) Mislow, K., private communication. For a discussion of the method used, see: Baum, M. W.; Guenzi, A.; Johnson, C. A.; Mislow, K. *Tetrahedron Lett.* **1982**, *23*, 31.

(10) We are indebted to Mark Wisnowsky (Owens-Corning Co.) for the determination of these spectra.

(11) Ermer, O. *Angew. Chem., Int. Ed. Engl.* **1977**, *6*, 411.

(12) This research was made possible by the generous financial support of the National Institutes of Health (Grant AI-11490). We thank Dr. Ole Mols for his invaluable assistance in recording the high-field NMR data.

Total Synthesis of (±)-Pentalenene

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The antibiotic properties of pentalenolactone,[1] an agent active against Gram-positive/negative bacteria and pathogenic fungi as a consequence of its ability to inhibit glyceraldehyde 3-phosphate dehydrogenase,[2] served to elicit extensive investigation of its biosynthesis. Soon to follow was evidence in support of its mevalonoid origin[3] and isolation of the acidic biosynthetic intermediates pentalenolactone E,[4] G,[5] and H,[6] as well as pentalenic

(1) (a) Isolation: Koe, B. K.; Osbin, B. A.; Celmer, W. D. *Antibiot. Ann.* **1956–1957**, 672. Takeuchi, S.; Ogawa, Y.; Yonehara, H. *Tetrahedron Lett.* **1969**, 2737. Martin, D. G.; Slomp, G.; Mizsak, S.; Duchamp, D. J.; Chidester, C. G. *Ibid.* **1970**, 4901. Duchamp, D. J.; Chidester, C. G. *Acta Crystallogr., Sect. B* **1972**, *B28*, 173. (b) Synthesis: Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. F. *J. Am. Chem. Soc.* **1978**, *100*, 6536; **1979**, *101*, 7020. Parsons, W. H.; Schlessinger, R. H.; Quesada, M. L. *Ibid.* **1980**, *102*, 889.

(2) Hartman, S.; Neeff, J.; Heer, U.; Mecke, D. *FEBS Lett.* **1978**, 339.

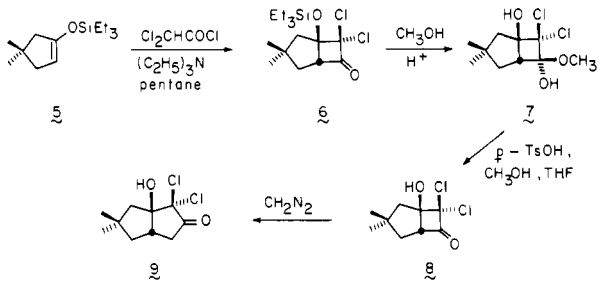
(3) Cane, D. E.; Rossi, T.; Pachlatko, J. P. *Tetrahedron Lett.* **1979**, 3639.

(4) (a) Isolation: Cane, D. E.; Rossi, T. *Tetrahedron Lett.* **1979**, 2973. (b) Synthesis: Paquette, L. A.; Schostarez, H.; Annis, G. D. *J. Am. Chem. Soc.* **1981**, *103*, 6526.

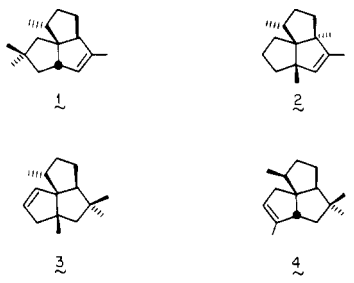
(5) Seto, H.; Sasaki, T.; Yonehara, H.; Uzawa, J. *Tetrahedron Lett.* **1978**, 923.

0002-7863/82/1504-4504$01.25/0

Scheme I



acid.[6] More recently, the less oxidized neutral precursor to these metabolites has been identified as **1** and named pentalenene.[7] This

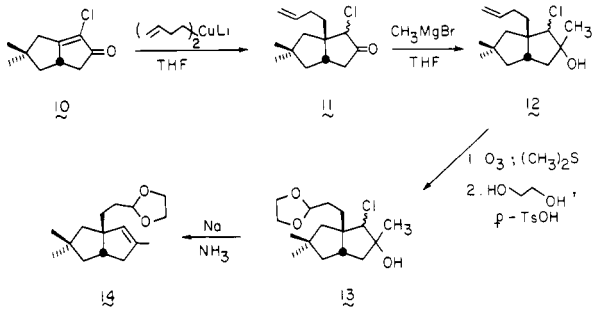


hydrocarbon, which is also derivable in low yield from the protoilludyl cation,[8] is structurally related to three other naturally occurring tricyclo[6.3.0.0^{4,8}]undecanes (**2–4**). Although several directed syntheses of isocomene (**2**)[9] have been devised,[10] comparable access routes to pentalenene (**1**), silphinene (**3**),[11] and senoxydene (**4**)[12] have yet to be reported. This hiatus in synthetic activity appears to be attributable to the widely differing positional arrangements of the double bonds and methyl groups, as well as the stereodisposition of the latter in these triquinanes,[13] which necessitates that each target be accorded a different strategy.

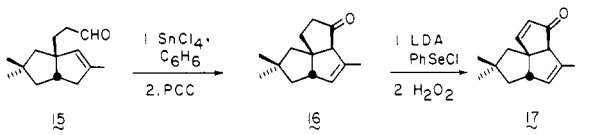
We have sought an efficient approach to pentalenene and in this communication report a scheme that successfully utilizes both chlorine atoms of a dichloroketene adduct for the regiospecific introduction of pivotal double bonds. In this manner, elaboration of the ring junction quaternary center and three angularly fused cyclopentane rings in **1** can be achieved attractively without concurrent formation of undesirable byproducts.

Silyl enol ether **5** (Scheme I), readily available through hydrosilation of 4,4-dimethyl-2-cyclopentenone,[14] underwent smooth condensation with dichloroketene[15] to furnish cyclobutanone **6** in 83% yield.[16] Because direct acid hydrolysis (*p*-TsOH, CH_3OH, THF) of **6** afforded an inseparable mixture of hexaethyldisiloxane and **8** (a substance labile to chromatography and heat), recourse was made to a two-step procedure. Simple dissolution of **6** in acidic

Scheme II



Scheme III



methanol gave hemiketal **7**, thereby providing a splendid opportunity for removing the admixed highly volatile methoxytriethylsilane under vacuum. Subsequent exposure of **7** to acid delivered **8**, which was directly ring expanded in the presence of diazomethane.[17] The resulting highly crystalline cyclopentanone **9**, mp 122.5–123.5 °C, could be isolated in 52% overall yield from **6**.

With this highly functionalized diquinane in hand, the stage was set for regiocontrolled introduction of a double bond as in **10** (Scheme II), and this was achieved by exposure of **9** to zinc dust in acetic acid at room temperature.[17] The α-chloro enone, isolated in quantitative yield, proved receptive to conjugate addition with lithium bis(3-butenyl)cuprate[18] (76%).[19] Entry of the new alkenyl substituent from a direction cis to the angular hydrogen is, of course, guaranteed by kinetic and thermodynamic factors.

At this point, we chose to introduce one of the two missing methyl groups. Methylmagnesium bromide addition to **11** provided a mixture of isomers (**12**) which were not separated because the chiral center just generated was soon to be returned to sp^2-hybridized status. To establish the third cyclopentane ring, we next subjected **12** to sequential ozonolysis and acetalization (58% overall from **11**). Reductive elimination (Na, NH_3) of the chlorohydrin functionality in **13** proceeded with regiospecific introduction of a double bond[20] to produce **14** in 59% yield.

Formation of aldehyde **15** (66%) (Scheme III) followed directly upon mild hydrolysis with pyridinium tosylate in aqueous acetone.[21] Under these conditions, partial conversion (ca. 15%) to a 1:1 mixture of two epimeric tricyclic alcohols occurred as well. The ^{1}H NMR spectra of the individual alcohols clearly indicated that installation of the third five-membered ring had proceeded with exceptional regiochemical control to produce only the internal double bond isomer. Independent cyclization of **15** with stannic chloride in benzene at 5–10 °C[10a] was particularly efficient in delivering only the endo alcohol (94%). Ketone **16** was obtained by PCC oxidation of either the exo or endo alcohol (96%).

Following the formation of **17** by kinetically controlled selenation of **16** and selenoxide elimination (64%),[22] conjugate addition of lithium dimethylcuprate provided a single adduct in 87.5% yield. Since subsequent Wolff–Kishner reduction of this ketone with hydrazine hydrate and potassium carbonate in triethylene glycol

(6) (a) Isolation: Seto, H.; Sasaki, T.; Uzawa, J.; Takeuchi, S.; Yonehara, H. *Tetrahedron Lett.* **1978**, 4411. (b) Synthesis: Sakai, K.; Ohtsuka, T.; Misumi, S.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1981**, 355.

(7) Seto, H.; yonehara, H. *J. Antibiot.* **1980**, *33*, 92.

(8) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 2869.

(9) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456. Zalkow, L. H.; Harris, R. N., III; Burke, N. I. *J. Natl. Prod.* **1979**, *42*, 96. Bohlmann, F.; Le Van, N.; Pickhardt, J. *Chem. Ber.* **1977**, *110*, 3777.

(10) (a) Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979**, *44*, 4014; *J. Am. Chem. Soc.* **1981**, *103*, 1835. (b) Oppolzer, W.; Bättig, K.; Hudlicky, T. *Helv. Chim. Acta* **1979**, *62*, 1493; *Tetrahedron* **1981**, *37*, 4359. (c) Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130. **1981**, *103*, 82. (d) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103. (e) Wender, P. A.; Dreyer, G. B. *Tetrahedron* **1981**, *37*, 4445.

(11) Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259. Subsequent to the submission of this paper, a total synthesis of (±)-silphinene was completed: Leone-Bay, A.; Paquette, L. A., submitted for publication.

(12) Bohlmann, F.; Zdero, C. *Phytochemistry* **1979**, *18*, 1747.

(13) Paquette, L. A. *Forschr. Chem. Forsch.* **1979**, *79*, 41.

(14) Exon, C.; Nobbs, M.; Magnus, P. *Tetrahedron* **1981**, *37*, 4515.

(15) Brady, W. T.; Lloyd, R. M. *J. Org. Chem.* **1980**, *45*, 2025.

(16) The initial report dealing with the regiochemistry of this [2 + 2] cycloaddition [Rasmussen, J. K. *Synthesis* **1977**, 91, citation of data reported in footnote 57] is decidedly in error.

(17) Greene, A. E.; Deprês, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 4003. Deprês, J.-P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036.

(18) Prepared from 3-butenyllithium [Cunico, R. F.; Han, Y.-K. *J. Organomet. Chem.* **1979**, *174*, 247] and the cuprous bromide–dimethyl sulfide complex.

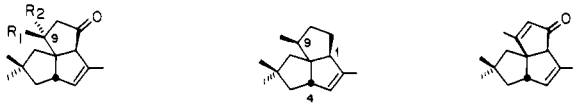
(19) Attempts to perform the conjugate addition with cuprates prepared from Grignard reagents gave mixtures of products as yet unidentified.

(20) Barluenga, J.; Yus, M.; Bernad, P. *J. Chem. Soc., Chem. Commun.* **1978**, 847.

(21) Sterzycki, R. *Synthesis* **1979**, 724.

(22) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

at 250 °C[23] led cleanly to *epi*-pentalenene (**19**, 83%),[24] delivery



18 a, $R_1 = CH_3$, $R_2 = H$; b, $R_1 = H$, $R_2 = CH_3$ — **19** — **20**

of the methyl group to **17** must have occurred from the β face to give **18a**. Since the stereochemistry of the 9-methyl group did not appear to be controlled by the convexity of the triquinane ring system, **20** was prepared from **18a** as before (57%) and reduced with lithium in liquid ammonia. Again **18a** was produced exclusively, and identical results were realized with CuH.[25] $NaHFe(CO)_4$,[26] $NaHTe$,[27] $NaHFe_2(CO)_8$,[28] and $Pd/(C_2H_5)_3N/HCOOH$[29] were ineffective as reducing agents. Only when recourse was made to the sterically bulky reagent combination $(Ph_3P)_3RhCl/C_2H_5SiH$[30] was kinetic control found not to strictly parallel thermodynamic control (**18a**/**18b** 2.24:1, 67%). Although these epimers can be separated by VPC,[31] it proved more convenient to arrive at **1**[32] by subjecting the epimeric ketone mixture directly to Wolff–Kishner reduction (59%).

In summary, the first directed total synthesis of pentalenene has been achieved. The demonstration that this sesquiterpene possesses the less stable configuration at C_9 not only lends credence to its proposed biosynthesis[7,8] but also emphasizes the need for equilibration studies in angular tricyclopentanoids of this type.

Acknowledgment. This research was generously financed by the National Cancer Institute (Grant CA-12115) and the Eli Lilly Co.

Registry No. (±)-**1**, 82442-49-7; **5**, 82253-47-2; (±)-**6**, 82352-47-4; (±)-**7**, 82352-48-5; (±)-**8**, 82352-49-6; (±)-**9**, 82352-50-9; (±)-**10**, 82352-51-0; (±)-**11**, 82352-52-1; **12**, 82352-53-2; **13**, 52352-54-3; (±)-**14**, 82352-55-4; (±)-**15**, 82352-56-5; (±)-**16**, 82352-57-6; (±)-**16** alcohol, isomer 1, 82352-58-7; (±)-**16** alcohol, isomer 2, 82398-55-8; (±)-**17**, 82352-59-8; (±)-**18a**, 82352-60-1; (±)-**18b**, 82398-56-9; (±)-**19**, 82398-57-0; (±)-**20**, 82352-61-2; $Cl_2CHCOCl$, 79-36-7; lithium bis(3-butenyl)cuprate, 71266-06-3; methyl bromide, 74-83-9.

(23) Hansen, H.-J.; Sliwka, H.-R.; Hug, W. *Helv. Chim. Acta* **1979**, *62*, 1120.
(24) ^1H NMR (300 MHz, $CDCl_3$) δ 0.958 (9-CH_3), 2.633 (H_1), 2.924–2.866 (H_4); ^{13}C NMR ($CDCl_3$, ppm) 140.58, 131.33, 64.03, 63.53, 54.90, 50.59, 46.32, 45.07, 39.75, 33.03, 31.49, 29.18, 28.57, 15.23, 13.44.
(25) Osborn, M. E.; Pegues, J. F.; Paquette, L. A. *J. Org. Chem.* **1980**, *45*, 167.
(26) Noyori, R.; Umeda, I.; Ishigama, T. *J. Org. Chem.* **1972**, *37*, 1542.
(27) Yamashita, M.; Kato, Y.; Suemitsu, R. *Chem. Lett.* **1980**, 847.
(28) Collman, J. P.; Finke, R. G.; Matlock, P. L.; Wahren, R.; Komoto, R. G.; Brauman, J. I. *J. Am. Chem. Soc.* **1978**, *100*, 1119.
(29) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3985.
(30) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1972**, 5035.
(31) The column used consisted of 25% Carbowax 20M on Chromosorb P (210 °C).
(32) The following spectral parameters were identical with those of racemic synthetic material prepared by Shirahama's method[8] and provided to us by Professor David Cane: ^1H NMR (300 MHz, $CDCl_3$) δ 0.916 (9-CH_3), 2.566 (H_1), 2.716–2.633 (H_4); ^{13}C NMR ($CDCl_3$, ppm) 140.52, 129.51, 64.77, 62.12, 59.38, 48.96, 46.85, 44.60, 40.51, 33.55, 29.98, 29.13, 27.63, 16.98, 15.45.

Additions and Corrections

Dynamic FTNMR Studies of Hindered Metal–Cage Rotation in Twelve-Vertex *closo*-Phosphinometallacarborane Complexes [*J. Am. Chem. Soc.* **1981**, *103*, 2988]. TODD B. MARDER, R. THOMAS BAKER, JUDITH A. LONG, JAMES A. DOI, and M. FREDERICK HAWTHORNE.*

Page 2992: In Table II, replace references to footnote "*b*" with "*d*" for all entries following "IIc" in column 1 under the heading "complex".

Page 2992: In Table III, replace entry "IIh" in column 1 under the heading "complex" with "IIi". Also amend footnote "*a*" to read—"Calculated from $^{31}P\{^1H\}$ NMR spectra; units of $\Delta G^{\ddagger}$ are kcal/mol; for error limits in $\Delta G^{\ddagger}$ see Experimental Section.

Book Reviews

Flavins and Flavoproteins. Proceedings of the 6th International Symposium on Flavins and Flavoproteins. Edited by Kunio Yagi and Toshio Yamano. Japan Scientific Societies Press, Tokyo, and University Park Press, Baltimore. 1980. xvi + 740 pp. $79.50.

This book consists of 79 papers that were presented at the symposium. They cover a wide range of subjects, including coenzyme substrate analogs; covalently and noncovalently bound flavin/protein interactions; complex flavoproteins; reactive intermediates of flavoproteins; flavoprotein-dependent oxygen, hydrogenation, and dehydrogenation activity; and flavoproteins in mixed function oxidase systems. The chemical aspects of flavin action, their metabolism, and their biosynthesis are also discussed. The papers presented contain photographs, spectra (UV, ^{13}C and ^1H NMR, EPR, CD), x-ray crystal structures, and mechanistic schemes. No experimental sections are included but the papers are thoroughly referenced. Among the papers presented are most of the major review articles in this field. This book includes a subject index.

This book is an excellent overview of the chemical as well as biological approaches that are being taken in order to further elucidate the mechanism of flavin catalysis.

L. A. Baron, *University of Michigan*

Atomic Energy Levels. By S. Fraga and K. M. S. Saxena (University of Alberta). Elsevier Scientific Publishing Company, Amsterdam and New York. 1979. x + 482 pp. $95.00.

This book presents a tabulation of atomic average energies, Slater–Condon integrals, and spin–orbit constants for a variety of electronic configurations. The data are given in the form of Z-polynomial least-squares expansion coefficients for the isoelectronic series of boron through uranium, while actual values of the quantities are given for the series of neptuium through nobrlium. The authors have not only provided a thorough description of the tables but they have also included a well-documented computer program to demonstrate how the data can be used in the semiempirical analysis of atomic spectra. As an example, a calculation of the spectrum of iron is given.

This book along with other books in this series provides a wealth of data on atomic systems and their properties.

Libero J. Bartolotti, *University of North Carolina*

Basic Biochemistry. Fourth Edition. By M. Rafelson, Jr., J. Hayashi, and A. Bizkorovainy (Rush College of Health Sciences). Macmillan Publishing Co., New York. 1980. vii + 418 pp. $14.95.

This textbook is a limited-scope, economical, soft-cover edition that attempts to fill the need for this type of text in biochemistry and would be suitable for an undergraduate or survey course. However, the text has a medical orientation which is unfortunate, because some biochemistry courses for which this book would be suited may have a broader outlook. The selection of chapter topics adequately covers the essentials of biochemistry and the chapters are for the most part acceptably written. For example, the sections on enzymes and carbohydrate chemistry are done well, and the chapters on protein chemistry and amino acid and protein metabolism may even be a bit overly ambitious. The only chapter that is badly done is one entitled Bioenergetics, which is both inadequate and misdirected. In addition, the discussion on DNA replication is not current. Occasionally the use of figures and tables in this text is confusing or of questionable application. A number of examples of this can be found throughout the text.

In conclusion, this text would be suitable for an undergraduate level biochemistry course with a strong medical orientation.

Ralph G. Eilberg, *University of Detroit*