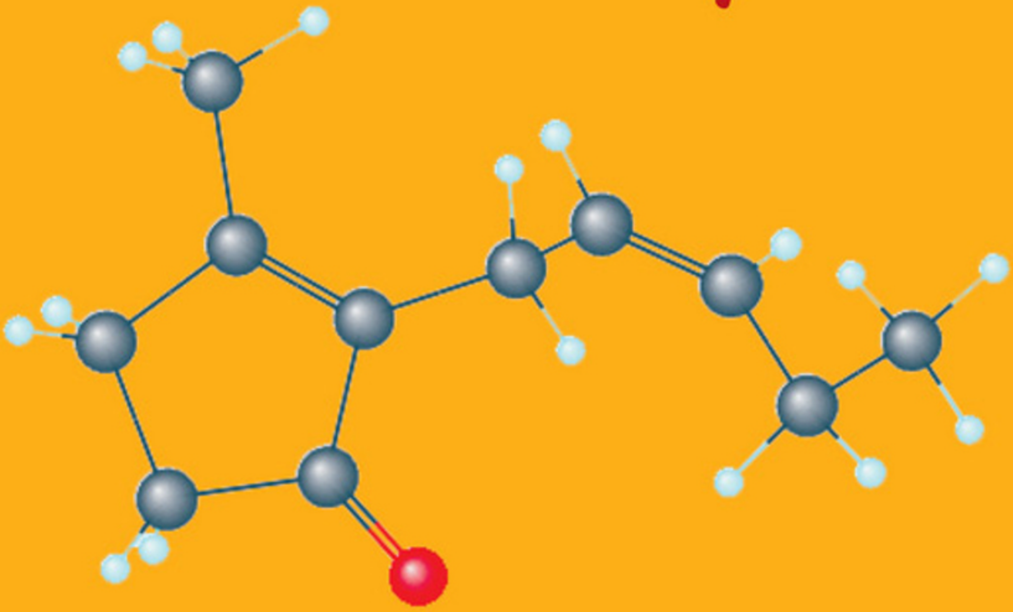
Third Edition

Intermediate Organic Chemistry



Ann M. Fabirkiewicz • John C. Stowell

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INTERMEDIATE ORGANIC CHEMISTRY

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Third Edition

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PREFACE TO THE THIRD EDITION

When I read the first edition of Stowell's *Intermediate Organic Chemistry*, I knew I had found an ideal text for a one-semester advanced organic chemistry course. The text was manageable in one semester, and the extensive references into the primary literature served as an introduction for students interested in pursuing organic chemistry in greater depth and made the text a useful reference beyond the scope of the course.

In this revision, I tried to stay true to the features that attracted me to the text initially, well described in Professor Stowell's preface to the second edition. The organization of the book remains much the same. The chapter on mechanisms has been moved to early pages of the book, as has been the chapter on pericyclic reactions. My inclination is to teach mechanisms early as a foundation for the study of reactions, but all the chapters have been written with the intent that they can be introduced to the student in any order. As much as possible, open source materials are cited allowing students ready access to the original literature, but at the same time, the early work on a topic is found in older literature and that historical value is recognized. The second chapter has been completely rewritten to focus on internet accessible resources. The last chapter has also been completely rewritten to focus on a survey of organic spectroscopy.

I have tried to make this text as error free as possible, knowing the frustration of a missing or mistaken reference, or a bond misplaced in a chemical structure. I welcome input from readers of this text. Please contact me directly at afab@randolphcollege.edu.

I want to thank my husband Steve for his patience and support during the preparation of this manuscript. My son Adam is a source of support and insight. My mom is an inspiration. My colleague Abraham Yousef at Sweet Briar College was helpful in obtaining Figures 10.6 and 10.14. Jonathan Rose and the team at Wiley have been responsive to all my questions and their assistance is invaluable. The support of my family and colleagues has made this work possible.

Lynchburg, Virginia
April 2015

ANN M. FABIRKIEWICZ

PREFACE TO THE SECOND EDITION

Consider the typical student who, having finished the two-semester introductory course in organic chemistry and then picking up an issue of the *Journal of Organic Chemistry*, finds the real world of the practicing chemist to be mostly out of reach, requiring a higher level of understanding. This text is intended to bridge that gap and equip a student to delve into new material.

There are two things to know while studying organic chemistry. One is the actual chemistry, that is, the behavior of compounds of carbon in various circumstances. The other is the edifice of theory, vocabulary, and symbolism that has been erected to organize the facts. In first-year texts, there is an emphasis on the latter with little connection to the actual observables. Thus students are able to answer subtle questions about reactions without knowing quite how the information is obtained. Chemistry is anchored in observations of specific cases, which can be obscured by the abstractions. For this reason, this text includes specific cases with more details and literature references to illustrate the general principles. Understanding these cases is an exercise to ensure the understanding of those general principles in a concrete way.

Many of the problems begin with raw data and require multistep thinking. Therefore, the student must solve a problem from the beginning rather than from a half-finished setup, and more thought and puzzling is necessary.

This book is selective. Out of the endless possibilities of reactions, a specific limited criteria were chosen and the chapters are consistent within that criteria. Likewise, the problems in the chapters were chosen selectively that fulfils the criteria, as well as reactions from the introductory organic courses. These selections were made based on the number of times they appeared in many current journal articles. Review references are given to aid a student who wishes to go further with these topics. Subjects that are generally well covered in introductory courses are either omitted or briefly reviewed here. Advanced topics are treated to a functional level but not exhaustively.

For those familiar with the first edition, you will find that major changes have been made in all the chapters. New examples have been added and many others have been replaced with better ones. The explanations have been elaborated and illuminated with more detail. The same 10 chapters have been retained, but new sections have been added and material reorganized. Substantial update has been done including stereochemical terminology, and the NMR chapter has been reframed in terms of pulsed high-field spectrometers. About twice as many exercise problems are available at the end of most chapters.

New Orleans, Louisiana
October 1993

JOHN C. STOWELL

PREFACE TO THE FIRST EDITION

Consider a typical student who has finished a two-semester introductory course in organic chemistry and then picks up an issue of the *Journal of Organic Chemistry*. He or she finds the real world of the practicing organic chemist to be mostly out of reach, on a different level of understanding. This text is intended to bridge that gap and equip a student to delve into new material.

There are two things to know while studying organic chemistry. One is the actual chemistry, that is, the behavior of compounds of carbon in various circumstances. The other is the edifice of theory, vocabulary, and symbolism that has been erected to organize the facts. In first-year texts, there is an emphasis on the latter with little connection to the actual observables. Thus students are able to answer subtle questions about reactions without knowing quite how the information is obtained. Chemistry is anchored in observations of specific cases, which can then be obscured by the abstractions. For this reason, this text includes specific cases with more details and literature references to illustrate the general principles. Understanding these cases is also an exercise to ensure the understanding of those principles in a concrete way.

This book is by necessity a selection. Subjects that are generally well covered in introductory texts are omitted or briefly reviewed here. Advanced topics are treated to a functional level, but not exhaustively. Specifically, the subjects are those necessary for understanding and searching the literature and some topics that are the elements of many current journal articles. The outcome is a selected sampling on a scale with latitude for creative lecturers to amplify with their own selections. Advanced texts give much attention to classical work that led to modern understanding. This text, with all due respect to the originators, does not cover that familiar ground but again covers current examples grounded in those classical ideas with modern interpretation.

There is a modicum of arbitrariness in the selections, and, considering this text as a new experiment, the author would welcome suggestions for substitutions and improvements.

New Orleans, Louisiana JOHN C. STOWELL
November 1987

1

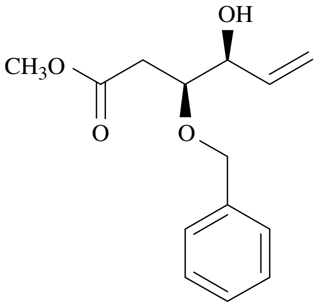
READING NOMENCLATURE

Organic chemistry is understood in terms of molecular structures as represented pictorially. Cataloging, writing, and speaking about these structures require a nomenclature system, the basics of which you have studied in your introductory course. To go further with the subject, you must begin reading journals, and this requires understanding of the nomenclature of complex molecules. This chapter presents a selection of compounds to illustrate the translation of names to structural representations. The more difficult task of naming complex structures is not covered here because each person's needs will be specialized and can be found in nomenclature guides [1–5]. Most of the nomenclature rules are used to eliminate alternative names and arrive at a unique (or nearly so) name for a particular structure; thus, when beginning with names, you will need to know only a small selection of the rules in order to simply read the names and provide a structure. Although the subject of nomenclature is vast, these selections will enable you to understand many names in current journals.

Intermediate Organic Chemistry, Third Edition. Ann M. Fabirkiewicz and John C. Stowell.

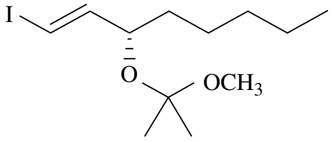
1.1 ACYCLIC POLYFUNCTIONAL MOLECULES

Methyl (3*S*,4*S*)-4-hydroxy-3-(phenylmethoxy)hex-5-enoate



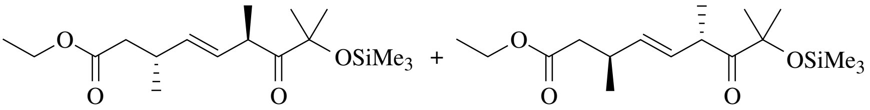
The space after methyl and the "ate" ending tells you this is a methyl ester. The acid from which the ester derives is a six-carbon chain with a double bond between carbons 5 and 6. There is an alcohol function on carbon 4. There is a methoxy group on carbon 3 and a phenyl group on the carbon of the methoxy group. Carbons 3 and 4 are stereogenic atoms each with *S* configuration as designated.

3-(*S*)-*trans*-1-Iodo-1-octen-3-ol methoxyisopropyl ether



This is an example of a derivative name, that is, the first word is the complete name of an alcohol and the other two words describe a derivatization where the alcohol is converted to an ether (ketal). Such a name would be useful in discussing a compound that has the ketal present as a temporary entity, for example, as a protecting group.

Ethyl (*E*,3*R**,6*R**)-3,6,8-trimethyl-8-[(trimethylsilyl)oxy]-7-oxo-4-nonenoate

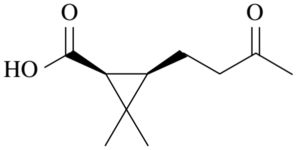


R,R *S,S*

This is the ethyl ester of a nine-carbon unsaturated acid with substituents. The *oxo* indicates that there is a keto function on carbon 7. Be careful to distinguish this from the prefix *oxa*-, which has a different meaning; see Section 1.6. The asterisks indicate that the configuration designation is not absolute but rather represents that stereoisomer and/or the enantiomer thereof. Thus this name represents the *R,R* and/or the *S,S* isomers, but not *R,S* or *S,R*. This designation excludes diastereomers and is a common way to indicate a racemate.

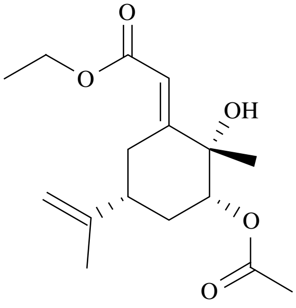
1.2 MONOCYCLIC ALIPHATIC COMPOUNDS

(1*S*,3*R*)-2,2-Dimethyl-3-(3-oxobutyl)cyclopropanecarboxylic acid



The ring is placed in the plane of the paper. Numbering of the ring starts at the location of the highest priority substitution, the carboxylic acid in this case. The butyl substituent on the third carbon of the ring has a keto function on the third carbon of the butyl chain.

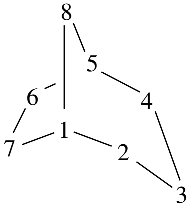
[2*S*-(1*E*,2α,3α,5α)]—[3-(Acetyloxy)-2-hydroxy-2-methyl-5-(methylethenyl) cyclohexylidene]acetic acid ethyl ester



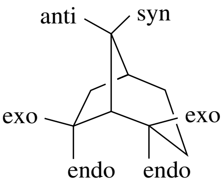
The *ylidene* indicates that the cyclohexyl is attached to the acetic acid by a double bond and the ethyl ester is indicated at the end for simplicity. The double-bonded ring atom is carbon 1 and the substituents on the ring are placed on the ring according to their locant numbers. The *E* indicates the geometry of the double bond. All the α substituents reside on one face of the ring, cis to each other. Any β substituents would reside on the opposite face of the ring, trans to the α substituents. Where two substituents are on the same ring atom, as on carbon 2 in this case, the Greek letter indicates the position of the higher-priority substituent. Here the hydroxy, acetyloxy, and methylethenyl are all cis to each other on the ring.

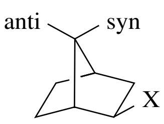
1.3 BRIDGED POLYCYCLIC STRUCTURES

The nomenclature of bridged polycyclic systems requires additional specifications. A bicyclic system would require two bond breakings to open all the rings, a tricyclic system, three, and so on. Rather than viewing this as rings, certain carbons are designated as bridgeheads from which the bridges branch and recombine. In the system below, the first bridgehead is designated as carbon 1 and the system is numbered around the largest bridge to the second bridgehead, carbon 5. Numbering continues around the medium bridge, then the smallest bridge, as shown. The compound is named bicyclo[3.2.1]octane.

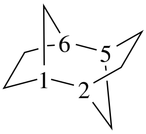


All bicyclo compounds require three numbers in brackets, tricyclo require four, and so on, and these numbers indicate the number of carbons in the bridges and are used to locate substituents, heteroatoms, and unsaturation. The name of the parent alkane includes the total number of atoms in the bridges and bridgeheads (excluding substituents) and is given after the brackets. The use of prefixes *exo, endo, syn*, and *anti* to indicate stereochemical choices is demonstrated generally as shown below.

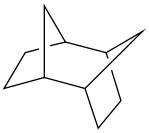




In tricyclic compounds, the relative stereochemistry among the four bridgeheads requires designation. Look at the largest possible ring in the molecule and consider the two faces of it. If there are no higher-priority substituents on the primary bridgehead atoms, the smallest bridge (but not a zero bridge) defines the α face. If the smallest bridge (not zero) at the secondary bridgeheads is on the same face of the large ring as the α defining one, it is also designated as α; that is, the two are cis to each other.



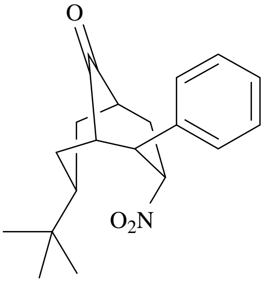
1α,2β,5β,6α



1α,2α,5α,6α

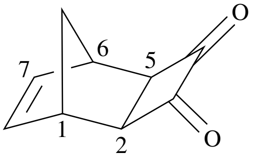
If they are trans, there will be two αs and two βs as illustrated. If there is a zero bridge, the position of the bridgehead hydrogens is indicated with Greek letters.

[1*S*-(2-*exo*,3-*endo*,7-*exo*)]-7-(1,1-Dimethylethyl)-3-nitro-2-phenylbicyclo [3.3.1]nonan-9-one



This bicyclo system has bridges with three, three, and one carbons each, indicated by the bracketed numbers separated by periods. Carbon 2 carries a phenyl that projects toward the smaller neighboring one-carbon bridge rather than the larger three-carbon bridge, as indicated by 2-*exo*. The 1,1-dimethylethyl group is also exo. This group is commonly called *tert-butyl*, but this is a *Chemical Abstracts* name built on linear groups. The prefixes *exo* and *endo* indicate the stereochemistry.

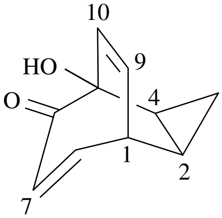
(1α,2β,5β,6α)-Tricyclo[4.2.1.$0^{2,5}$]non-7-ene-3,4-dione



Starting with a pair of bridgeheads, draw the four-, two-, and one-carbon bridges. The zero bridge then connects carbons 2 and 5 as indicated by the superscripts, thus making them bridgeheads also. At bridgeheads 1 and 6, the smallest bridge is considered a substituent and given the α designation at both ends. At bridgeheads 2 and 5, the βs indicate that the hydrogens are trans to the α bridge.

Sometimes a bridgehead substituent will have a higher priority than the smallest bridge thereon. The designation for that bridgehead will indicate the position, α or β, of that higher-priority substituent rather than the bridge as illustrated in the next example.

(1α,2β,4β,5β)-5-Hydroxytricyclo[3.3.2.$0^{2,4}$]deca-7,9-dien-6-one

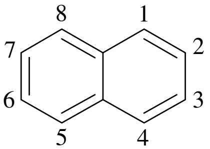


At bridgehead 1, the smallest bridge, carbons 9 and 10, is considered a substituent on the largest ring and designated α. The hydrogens at carbons 2 and 4 are trans to it and marked β. The OH group on carbon 5 is a higher-priority substituent than the C-9 to C-10 bridge and is trans to the bridge; thus it is labeled β.

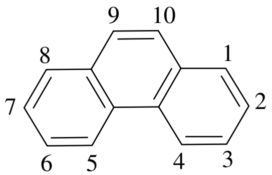
1.4 FUSED POLYCYCLIC COMPOUNDS

Fused-ring compounds have a pair or pairs of adjacent carbon atoms common to two rings. Over 35 carbocyclic examples have trivial names, some of which need to be memorized as building blocks for names of more complex examples. The names end with *ene*, indicating a maximum

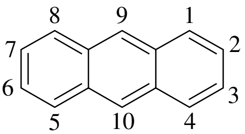
TABLE 1.1 Trivial Names of Some Fused Polycyclic Hydrocarbons



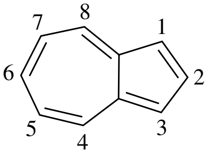
Naphthalene



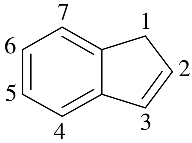
Phenanthrene[a]



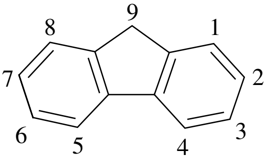
Anthracene[a]



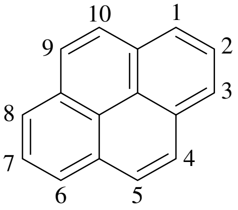
Azulene



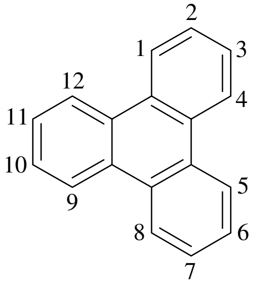
Indene



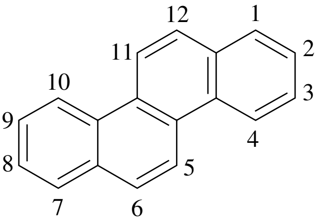
Fluorene



Pyrene



Triphenylene



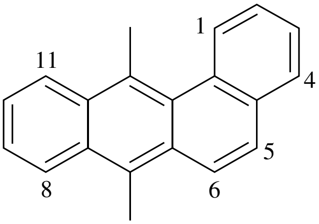
Chrysene

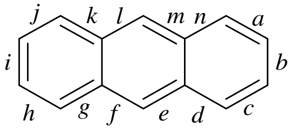
[a] Exceptions to systematic numbering.

number of alternating double bonds. A selection is illustrated in Table 1.1, showing one resonance form for each. Others can be found online [6].

Fusing more rings onto one of these basic systems may give another one with a trivial name. If not, a name including the two rings or ring systems with bracketed locants is used, as in the following example.

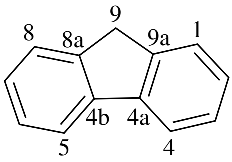
7,12-Dimethylbenz[*a*]anthracene



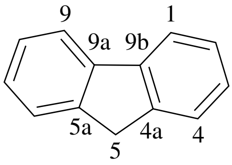


Since a side of the anthracene is shared, the sides are labeled *a, b, c*, and so on, where carbons numbered 1 and 2 constitute side *a* and 2 and 3 constitute side *b*, continuing in order for all sides. The earliest letter of the anthracene is used to indicate the side fused, and the ring fused to it appears first. The “o” ending of benzo is deleted here because it would be followed by a vowel.

The final combination is then renumbered to locate substituents, or sites of reduced unsaturation. To renumber, first orient the system so that a maximum number of fused rings are in a horizontal row. If there are two or more choices, place a maximum number of rings to the upper right. Then number clockwise starting with the carbon not involved in fusion in the most counterclockwise position in the uppermost–farthest right ring. See the numbering in the systems with trivial names above. Atoms at the fusion sites, which could carry a substituent only if they were not π-bonded, are given the number of the previous position with an a, b, c, and so on. Where there is a choice, the numbers of the fusion carbons are minimized too; for example, 4b < 5a:

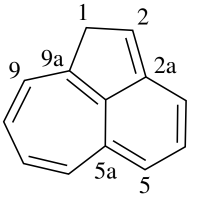


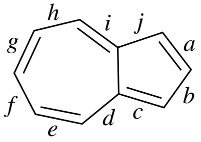
Correct



Incorrect

1*H*-Benz[*cd*]azulene

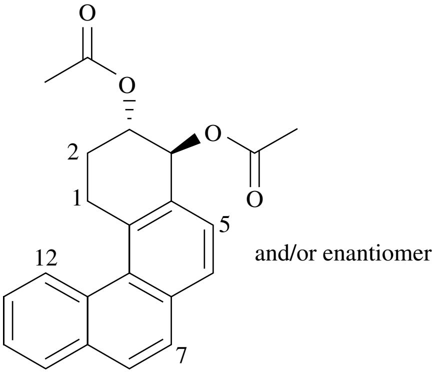




Azulene

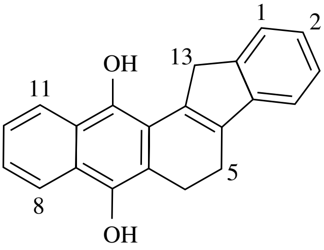
First letter the sides of azulene. The benzo ring is fused to both the *c* and *d* faces as indicated in the brackets. Now reorient the system for numbering. The choice of which two rings go on the horizontal axis and which one is in the upper position is determined by which orientation gives the smallest number to the first fusion atom—in this case 2a instead of 3a, or 4a. In molecules where one carbon remains without a double-bonding partner, it is denoted by *H*. This is called *indicated hydrogen* and is used even when an atom other than hydrogen is actually on that carbon in the molecule of interest.

trans-1,2,3,4-Tetrahydrobenzo[*c*]phenanthrene-3,4-diol diacetate



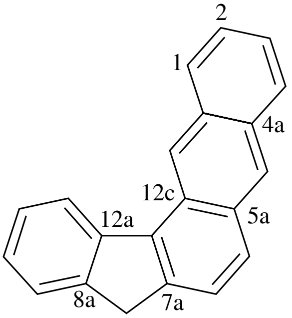
The sides of phenanthrene are lettered; the carbons numbered 3 and 4 are the *c* side. As in several systems, phenanthrene is numbered in an exceptional way. A benzene ring is fused to the *c* side, and a new systematic numbering is made. Carbons 1–4 have hydrogens added to saturate two double bonds, and then carbons 3 and 4 have hydroxy groups substituted for hydrogens in a trans arrangement. Finally, the compound is named as the acetate ester at both alcohol sites.

6,13-Dihydro-5*H*-indeno[2,1-*a*]anthracene-7,12-diol

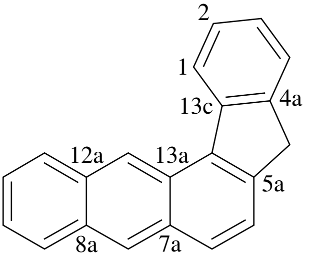


The fusion of this ring system is given in the brackets. The bracketed *a* precedes anthracene indicating that the sides of anthracene will be lettered, and the bracketed 2,1 follows the indene, thus the indene numbering indicated in Table 1.1 will be used to give the point of fusion. The order of the numbers indicates the direction of the fusion, thus the carbons of indene are fused in order 2, then 1 to the *a* side of anthracene, with the number 1 carbon of anthracene constituting the number 2 carbon of indene, and the number 2 carbon of anthracene, the number 1 carbon of indene. The united system is then renumbered according to the rules and the substituents, added hydrogen, and indicated hydrogen placed accordingly. The indicated hydrogen is assigned the lowest-numbered atom not involved in double bonding.

The other direction of fusion is in 1*H*-indeno[1,2-*a*]anthracene:



Correct:
4a, 5a, 7a, 8a, 12a, 12b, 12c, 13a



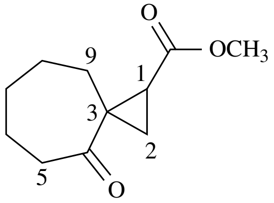
Incorrect:
4a, 5a, 7a, 8a, 12a, 13a, 13b, 13c

Note that here a different orientation is used because it gives the lower fusion numbers.

1.5 SPIRO COMPOUNDS

In spiro compounds, a single atom is common to two rings. There are two kinds of nomenclature for these. Where there are no fused rings present, the carbons of both rings are counted in one series as in the bicyclic nomenclature, and the hydrocarbon name includes the carbons of both rings as in the following example.

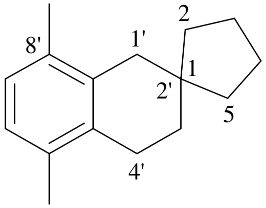
4-Oxospiro[2.6]nonane-1-carboxylic acid methyl ester



Of the nine carbons, one is the spiro atom, two join round to make a three-membered ring, and six finish a seven-membered ring, as indicated by the bracketed numbers. The locant numbers begin in the smaller ring at an atom adjacent to the spiro one, continue around the smaller ring including the spiro atom, and proceed around the larger ring.

When ring fusion is also present, the two ring systems that share the spiro atom are given in brackets with splicing locants as shown in the following example.

3′,4′-Dihydro-5′,8′-dimethylspiro[cyclopentane-1,2′(1′*H*)-naphthalene]



Two separate numbering systems are used. The unprimed number belongs to the ring nearest it in the brackets, the cyclopentane, while the primed numbers belong to their nearer neighbor in the brackets, naphthalene. The locant numbering in the fused system follows the usual pattern (Section 1.4) and is identified with primes. The -1,2′ indicates that the shared atom is number 1 of the cyclopentane ring and number 2′ of the naphthalene. The spiro linkage requires another naphthalene ring atom to be excluded from double bonding, in this case, the 1′ as determined by the indicated hydrogen, 1′*H*.

1.6 MONOCYCLIC HETEROCYCLIC COMPOUNDS

Systematic and trivial names are both commonly in use for heterocyclic compounds. The systematic names consist of one or more prefixes from Table 1.2 with multipliers where needed designating the heteroatoms, followed by a suffix from Table 1.3 to give the ring size with an indication of the unsaturation. This is preceded by substituents. Thus, oxepin is a

TABLE 1.2 Prefixes in Order of Decreasing Priority[a,b]

Oxygen	ox-
Sulfur	thi-
Selenium	selen-
Nitrogen	az-
Phosphorus	phosph- (or phosphor- before -in or -ine)
Silicon	sil-
Boron	bor-

[a] From Ref. [7].

[b] An “a” is added after each prefix if followed by a consonant.

TABLE 1.3 Suffixes Indicating Ring Size[a]

	Containing Nitrogen		Containing no Nitrogen	
Atoms in the Ring	Maximally Unsaturated	Saturated	Maximally Unsaturated	Saturated
3	-irine	-iridine	-irine	-irane
4	-ete	-etidine	-ete	-etane
5	-ole	-olidine	-ole	-olane
6	-ine	—[b]	-in	-ane
7	-epine	—[b]	-epin	-epane
8	-ocine	—[b]	-ocin	-ocane
9	-onine	—[b]	-onin	-onane
10	-ecin	—[b]	-ecin	-ecane
>10[c]	—	—	—	—

[a] From Ref. [7].

[b] Use the unsaturated name preceded by “perhydro.”

[c] Use the carbocyclic ring name with heteroatom replacement prefixes: oxa-, thia-, and so forth.