A Little About the Chemistry of Peroxides

(which can fight malaria, by the way)

Artemisinin

Yingzhaosu A

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Natural Peroxy Compounds

Fatty acid peroxyketals

\[ n-C_{16}H_{33} \underbrace{\text{MeO}}_{\text{chondrilline}} \underbrace{\text{CO}_2\text{Me}}_{\text{MeO}} \]

1,2-dioxane or dioxolane carboxylates

\[ \text{mycaperoxide A} \]

Mono- and sesquiterpenes

\[ \text{isolyratylhydroperoxide A} \]
Facts about Malaria

1. Scale
* Around 2.5 billion people (at least 40% of the world’s population) are at risk in over 90 countries
* Malaria causes or contributes to 3 million deaths and up to 500 million acute clinical cases each year. In other words: almost as many deaths per annum as the AIDS death total in the last 15 years
* 20 times more deaths each day than deaths from the 1995 EBOLA epidemic in Zaire (~250).
* Cause of more military casualties than bullets in every 20th century war in malarious regions
* The majority of deaths are children. In other words children are dying at a rate of 4 per minute, 5,000 a day and 35,000 a week.
* Other high risk groups include pregnant women, refugees, migrant workers, and non-immune travellers - over 20 million Western tourists at risk annually.
* The main areas affected are Africa, South East Asia, India and South America but surveillance and records are too poor to know the real distribution and case numbers.
* Malaria is one of leading causes of morbidity and mortality in the developing world (along with TB, acute respiratory syndrome, diarrhoea and HIV) but still not recognised in developed countries as a disaster like AIDS or EBOLA.

2. Resistance
* Drug resistance is increasing rapidly, largely due to widespread uncontrolled and unregulated drug distribution.
* Drugs have been used until resistance has rendered them ineffective, after which closely related drugs that are introduced show reduced efficacy and severely compromised life spans.
* Today, there are few effective anti-malarial drugs - most tropical countries still rely on chloroquine (which is increasingly ineffective) primarily due to cost and the limitation of alternatives.
* The vicious circle of new drug resistance limits research and rollout options and increases the cost of R&D - it is hard to establish whether to use new options widely, risking resistance, or keep them in reserve until resistance to existing drugs such as chloroquine or quinine becomes widespread.
* Another underlying factor contributing to the development of resistance is the improper usage of the drugs; for example, subcurative doses - people feel better, so stop taking their medicine, and some resistant parasites may be given the chance to survive and be transmitted by mosquitoes.
* There is insufficient research into novel drug targets. Current new options are based on the same three families of compounds (the quinolines, antifolates, and artemesinin derivatives) all of which have records of resistance and/or ineffectiveness. Insecticide programmes have also been hampered by the emergence of resistance to DDT and other insecticides.

http://www.malaria.org
Plasmodium falciparum

Anopheles - see how she sits!

falciparum: sporozoites exo-erythrocytic schizont

falciparum: merozoites bud from exo-erythrocytic schizonts

The infection is caused by a blood-dwelling apicomplexan parasite belonging to the genus Plasmodium (Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae cause human infections). The parasites are transmitted by blood-sucking female anopheline mosquitoes (more than 50 species are known vectors).

Malaria chemotherapy have been directed at killing the parasite when it has infected human erythrocytes. Starving the malaria parasite by blocking its digestion of human haemoglobin (e.g. using protease inhibitors) and poisoning the malaria parasite by blocking aggregation of toxic haeme into innocuous haemolysin are two areas of active research.

Also, killing the malaria schizonts in human erythrocytes has been achieved effectively with iron-activated peroxide drugs related to the natural herb-derived antimalarial peroxide artemisinin.

http://www.anaesthetist.com/icu/infect/malpix.htm
International Journal of Parasitology, 2002, 32, 1537
Some Antimalarial Drugs

WW2
Vietnam War

1000 years ago + Vietnam War
1,2,4-Trioxane-Type Antimalarial Agents

Artemisinin was isolated as a new antimalarial drug in 1972 in China.

*Artemisia annua* contains <0.1% (under special agricultural conditions).

- Poor oil or water solubility
- Short plasma half-life
- Poor oral activity

R=H, Me, Et, COCH₂CH₂CO₂Na, CH₂C₆H₄CO₂Na

Oil or water solubility
1,2,4-Trioxane-Type Antimalarial Agents

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- Poor oil or water solubility
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-C-O-O-C-O-C-O-C=O moiety may be responsible for the activity.

The interest in cyclic peroxides increased.

Oil or water solubility

R=H, Me, Et,
COCH₂CH₂CO₂Na,
CH₂C₆H₄CO₂Na
Ways to Generate Peroxides.

Photo oxidation

\[ \text{Sens} + \text{hv} \rightarrow ^1\text{Sens} \]
\[ ^1\text{Sens} \rightarrow ^3\text{Sens} \]
\[ ^3\text{Sens} + ^3\text{O}_2 \rightarrow \text{Sens} + ^1\text{O}_2 \]
\[ ^1\text{O}_2 + \text{A} \rightarrow \text{AO}_2 \]

Ways to Generate Peroxides.

Still Photo Oxidation

- Rose Bengal
- Benzophenone
- Tetraphenylporphine (TPP)

\[
\begin{align*}
\text{Sens} + \text{hv} & \rightarrow ^1\text{Sens} \\
^1\text{Sens} & \rightarrow ^3\text{Sens} \\
^3\text{Sens} + 3\text{O}_2 & \rightarrow \text{Sens}^*\text{O}_2 \\
\text{Sens}^*\text{O}_2 + \text{A} & \rightarrow \text{AO}_2
\end{align*}
\]

\[
\begin{align*}
\text{Sens} + \text{hv} & \rightarrow ^1\text{Sens} \\
^1\text{Sens} & \rightarrow ^3\text{Sens} \\
^3\text{Sens} + 3\text{O}_2 & \rightarrow \text{Sens} + ^1\text{O}_2 \\
^1\text{O}_2 + \text{A} & \rightarrow \text{AO}_2
\end{align*}
\]
Reactions of Singlet Oxygen

1. Ene-reaction

\[ \text{alkene} + {^1}O_2 \rightarrow \text{alkeneOOH} \]

2. 1,4-cycloaddition

\[ \text{alke} + {^1}O_2 \rightarrow \text{cycloaddition product} \]

Ireland, R.E. et al, JACS, 1970, 92, 5743
White, J.D. et al, JACS, 1976, 98, 634
Reactions of Singlet Oxygen 2.

Chiral Auxiliary.

![Chemical structures and reaction scheme]

**Table 1:** Diastereoselectivities in the Photooxygenation of Optically Active Sorbic Acid Amides 3

<table>
<thead>
<tr>
<th>entry</th>
<th>amide</th>
<th>R¹</th>
<th>R²</th>
<th>dr¹</th>
<th>l-4 : u-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>H</td>
<td>CH₂Ph</td>
<td>68:32</td>
<td>68:32</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>H</td>
<td>CH₂Nph</td>
<td>67:33</td>
<td>67:33</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>H</td>
<td>i-Pr</td>
<td>76:24</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>H</td>
<td>Ph</td>
<td>91:9</td>
<td>91:9</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>Me</td>
<td>CH₂Ph</td>
<td>≥95:5</td>
<td>≥95:5</td>
</tr>
</tbody>
</table>

*¹ Diastereomeric ratios determined by ¹H or ¹³C NMR analysis directly on the crude reaction mixtures, error ±5% of the stated values.

* Other enantiomer was used.  

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Wirth, T., et al. *JACS, 1998, 120, 4091*
Ways to Generate Peroxides.

Ozonolysis

R\textsubscript{1} R\textsubscript{2} O O

R\textsubscript{1} R\textsubscript{2} T\textgreater\textunderscore80\degree C

R\textsubscript{1} R\textsubscript{2} O O O

R\textsubscript{1} R\textsubscript{2} DCM, pentane, etc.

MeOH

R\textsubscript{1} OH R\textsubscript{1} OMe

R\textsubscript{2} + [3+2] retro [3+2] [3+2]

Ways to Generate Peroxides.

Ozonolysis

\[
\begin{align*}
\text{EtO}_2H + \text{O}_3 &\rightarrow \text{CH}_3\text{OCH}_2\text{OOH} \\
\text{Me}_2\text{C}=\text{CHCl} + \text{O}_3 &\rightarrow \text{CH}_3\text{COCH}_2\text{OOH} \\
\text{EtO} + \text{Me}_2\text{C}=\text{CHCl} + \text{O}_3 &\rightarrow \text{MeOCH}_2\text{CH}_2\text{OOH} \\
\end{align*}
\]

Ways to Generate Peroxides.

Other ways

Feldman, K. S. Synlett, 1995, 217
Reactions of Peroxides

Scheme 4. Synthesis of Plakinic Acid 1

1/1 mixture

(a) Me$_3$Al, Cp$_2$ZrCl$_2$, then acetaldehyde (70%); (b) PDC, DMF (91%); (c) H$_2$O$_2$, LiOH (19%); (d) 2-methoxyethanol, TsOH (79%); (e) CH$_2$=C(OTMS)SEt, TiCl$_4$ (54%); (f) LiOH, THF, H$_2$O, H$_2$O$_2$ (90%).

Reactions of Peroxides

\[
R_2\overset{\text{O}}{\text{Me}} + \text{HO}-\text{C} = \text{C} \rightarrow n=1-3
\]

\[
\text{O}_3 \rightarrow \text{HO} - \text{C} = \text{C} \rightarrow \text{OH}
\]

\[
1 - 3\% 13-67\%
\]

pathway 1

pathway 2

\[
\text{PPh}_3
\]
Even 8- and 9-membered rings can be made.

Total Synthesis of Artemisinin 1a

MOMCl, PhNMe₂, DCM
B₂H₆, THF

80% (+epimer 10%)

1. BnCl, KH
2. HCl, MeOH
3. PCC, DCM

73%
dr=6/1

Me₃Si

Li/OMe

Me₃Si

72%

Hofheinz*, W.; Schmidt, G. JACS, 1983, 105, 624
Total Synthesis of Artemisinin 1b

Hofheinz*, W.; Schmidt, G. JACS, 1983, 105, 624
Total Synthesis of Artemisinin 2a

Avery, M. A. et al JACS, 1992, 114, 974
Total Synthesis of Artemisinin 2b

Figure 1. Transoid (6a) and cisoid (6b) rotamers of the preferred conformation of aldehyde 6. Nucleophilic attack could be predicted to occur upon the less sterically encumbered \( \alpha \)-face of 6a to provide the C-1' S diastereomer 15.

Avery, M. A. et al JACS, 1992, 114, 974
Total Synthesis of Artemisinin 2c

Avery, M. A. et al JACS, 1992, 114, 974
Total Synthesis of Artemisinin 3a

1. THF, 0°C, 7 days
   - MeMeCy2BH

2. THF, 0°C
   - MeMeCy2BH
   - MeMeOH

3. MeMeOH

4. MeMeOH
   - CrO3/acetone
   - KI, I2, NaHCO3

5. MeMeOH
   - AIBN, PhMe, 110°C
   - Bu3SnH or Ph3SnH

6. MeMeOH
   - Ph2Se2/Br2, DCM
   - AIBN, PhMe, 110°C
   - Bu3SnH or Ph3SnH

Yadav, J.S. et al, ARKIVOC, 2003, 3, 125
Total Synthesis of Artemisinin 3b

Yadav, J.S. et al ARKIVOC, 2003, 3, 125

Total Synthesis of Artemisinin 3c

Yadav, J.S. et al ARKIVOC, 2003, 3, 125
Yingzhaosu A is an antimalarial constituent isolated from Yingzhao (*Artabotrys uncinatus* (L.) Merr.) in 1979.

Dioxabicyclo [3,3,1]-nonane ring system, Dihydroxy olefinic side chain.

C1, C4, C6 absolute configuration was known C8 and C12 were unresolved

Total Synthesis of (+)-Yingzhaosu A 1a

(R)-(-)-carvone

1. mCPBA, DCM
2. BF₃·Et₂O, PhH

MeCH₂
Me
O
(R)-(-)-carvone

1. MeMgBr, Et₂O, -78°C
2. POCl₃, Py

Me
CHO
Me
O

15%

O₂, hv, methylene blue
MeCN, TsOH

Me
Me
HO
O
O
O
Me
Me
O

Me
Me
Me
Me
O

1. HC(OMe)₃
2. POCl₃

MeO
OMe

Total Synthesis of (+)-Yingzhaosu A 1b

1. PtO₂, H₂(1equiv), EtOAc, 80%
2. TsOH, acetone/water

LiBH₄
dr=3/2

Me
Me
O
O
O O
O
Me
Me
O
O
O O
O
62%
The natural product geometry
By H-NMR and X-Ray

The absolute structure of (+)-Yingzhaosu A

Conclusions:

- Peroxy compounds are not so rare in nature
- They can be very stable to a variety of chemical conditions
- Many peroxides possess useful pharmacological properties
- Photo oxygenation and ozonolysis are the two major ways to produce them