UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVEN PHARMACEUTICALS, INC.
AND MYLAN PHARMACEUTICALS INC.,
Petitioners

v.

NOVARTIS AG AND LTS LOHMANN THERAPIE-SYSTEME AG,
Patent Owners

No. IPR2014-00549[1] (U.S. Patent No. 6,316,023)
No. IPR2014-00550[2] (U.S. Patent No. 6,335,031)[3]

PETITIONERS' DEMONSTRATIVES

[1] Case IPR2015-00265 has been joined with this proceeding.
[2] Case IPR2015-00268 has been joined with this proceeding.
[3] Petitioner Noven attests that the word-for-word identical paper is filed in each proceeding identified in the heading.

Pursuant to 37 C.F.R. § 42.70(b), Petitioner Noven Pharmaceuticals, Inc. files the attached demonstrative exhibits for oral hearing scheduled for June 2, 2015.

Dated: May 26, 2015

Respectfully submitted,

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Counsel for Petitioner Noven Pharmaceuticals, Inc.

Noven Pharmaceuticals, Inc. and Mylan Pharmaceuticals Inc., Petitioners

v.

Novartis AG and LTS Lohmann Therapie-Systeme AG, Patent Owner

No. IPR2014-00549 and IPR2014-00550[1] (citations to 550 IPR unless noted)
Patent Nos. 6,316,023 and 6,335,031
June 2, 2015

[1]Joined with IPR2015-00265 and IPR2015-00268

There is No Dispute That . . .

- Enz is a proper starting point for the obviousness analysis;
- All the elements of the challenged claims of the ’023 and ’031 patents are found in the prior art;
- The particular features of any dependent claim do not independently support patentability;
- It would have been routine work for a POSA to select an effective amount of an appropriate antioxidant;
- Evidence of secondary considerations has not been presented.

Paper 25 pp. 20-21; Paper 31 pp. 1, 3; Ex. 1031 ¶ 25 n.2.

Grounds for Institution '023 Patent

Reference(s)	Basis	Claims
Enz and the Handbook, optionally in view of Rosin and/or Elmalem and/or Ebert	§ 103(a)	1, 7
Enz and the Handbook, and/or Rosin, and/or Ebert	§ 103(a)	2
Enz and the Handbook and/or Ebert	§ 103(a)	4, 5
Enz, the Handbook, and Ebert or Kissel	§ 103(a)	8
Enz and Sasaki	§ 103(a)	1, 2, 4, 5, and 7
Enz, Sasaki, and Ebert or Kissel	§ 103(a)	8

IPR2014-00549 Institution Decision, Paper 10 p. 25.

Grounds for Institution '031 Patent

Reference(s)	Basis	Claims
Enz, the Handbook, Rosin, Elmalem, and Ebert	§ 103(a)	1, 2, 7, 15, and 18
Enz, the Handbook, Rosin, and Ebert	§ 103(a)	3 and 16
Enz and Sasaki	§ 103(a)	1–3, 7, 15, 16, and 18

IPR2014-00550 Institution Decision, Paper 10 p. 28.

’023 and ’031 Patent Claim 1

Claim 1 ’031 Patent

A pharmaceutical composition comprising:

(a) a **therapeutically effective amount** of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A);

(b) **about 0.01 to about 0.5 percent** by weight of an **antioxidant**, based on the weight of the composition, and

(c) **a diluent or carrier**.

Claim 1 ’023 Patent

A **pharmaceutical composition** comprising:

1 to 40 weight percent of (S) -N-ethyl-3-[(1-dimethylamino) ethyl]-N-methylphenyl carbamate in the form of a free base or acid addition salt;

0.01 to 0.5 weight percent of an **antioxidant**, and

a **diluent or carrier**,

wherein the weight percents are based on the total weight of the pharmaceutical composition.

IPR2014-00549, Ex. 1001; IPR2014-00549, Ex. 1001.

Other Claims of the ’023 and ’031 Patents

Method Claim

A method of stabilizing rivastigmine by combining rivastigmine with an amount of antioxidant effective to stabilize. (Claim 15, ’031 patent.)

Elements of Remaining Claims

- Specific antioxidants: tocopherol, ascorbic acid, BHT, BHA, propyl gallate;
- Narrowed antioxidant ranges;
- Elements of a transdermal system, including release liners, backing layer, adhesive.

IPR2014-00550, Ex. 1001; IPR2014-00549, Ex. 1001.

Person of Ordinary Skill

- Collaborative team of individuals;
- Included team members from a variety of disciplines involved in formulating pharmaceutical compounds;
- Familiar with pharmaceutical formulation development, including transdermals, and the conventional excipients employed therewith;
- Included organic chemist with sufficient knowledge to make predictions based on the chemical structure of a compound.

Paper 1 pp. 5-6; Ex. 1010 ¶ 31; Ex. 1011 ¶ 11; Ex. 1031 ¶¶ 13-14; Ex. 1032 ¶¶ 4-5.

A POSA Would Have Expected That Rivastigmine is Susceptible to Oxidative Degradation

- Based on the chemical structure of rivastigmine;
- Based on the similarity of rivastigmine's structure to nicotine, which was known to be susceptible to oxidation;
- Based on prior art, including Elmalem, Rosin, Sasaki, Ebert, and Enz.

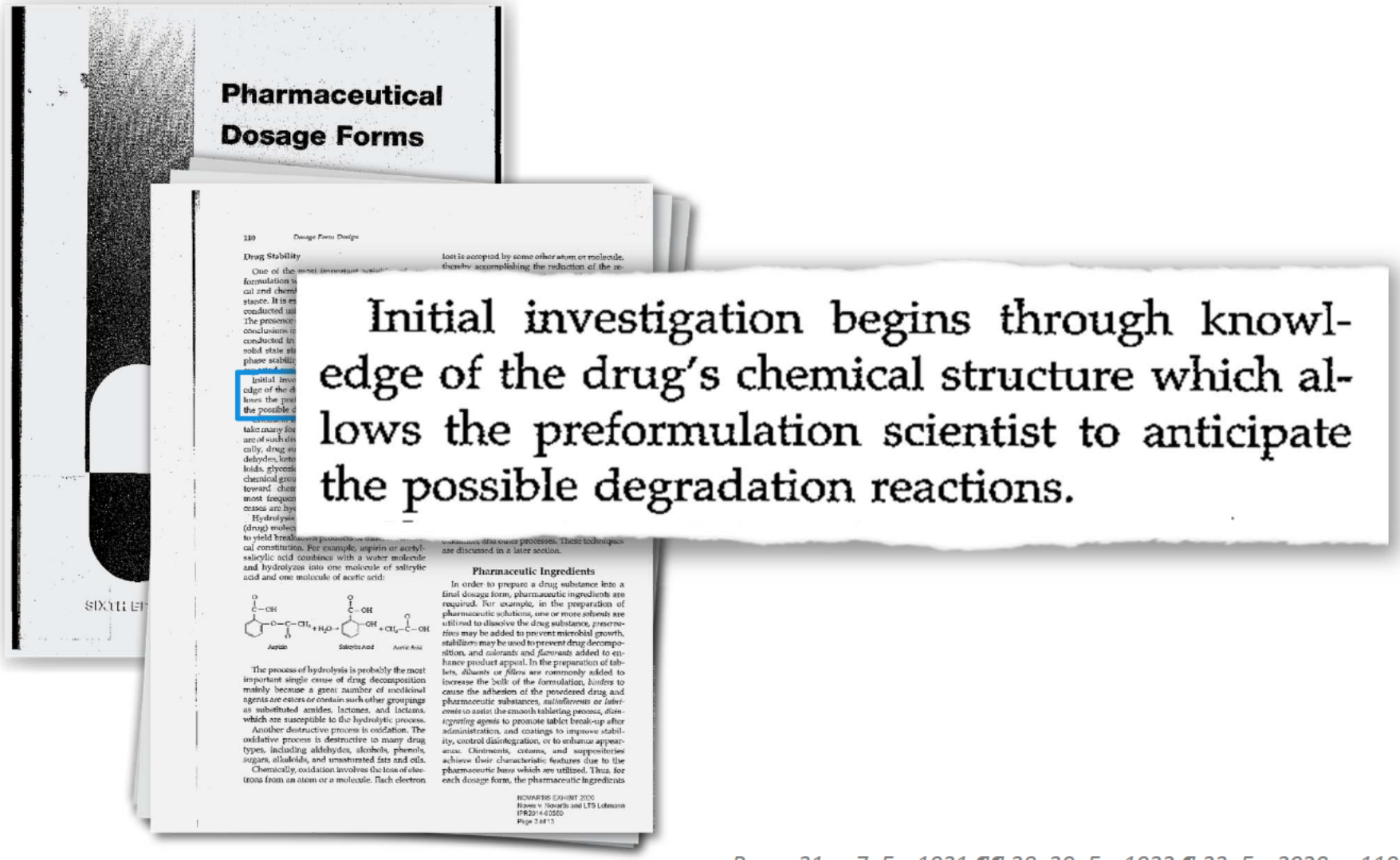
Paper 1 pp. 4, 32-36, 42-43, 46-47; Paper 31 pp. 4-9; Ex. 1010 ¶¶ 31, 63; Ex. 1011 ¶¶ 12, 53-59; Ex. 1031 ¶¶ 24-32; Ex. 1032 ¶¶ 22-67.

A POSA Would Have Reasonably Expected Rivastigmine to Oxidatively Degrade Based on Its Chemical Structure

- A POSA was instructed by the prior art to examine the structure of a molecule during preformulation and make predictive assessments;
- Applying functional group chemistry to anticipate potential modes of degradation;
- The mechanistic pathways of a reaction are different from the threshold question of susceptibility to oxidative degradation.

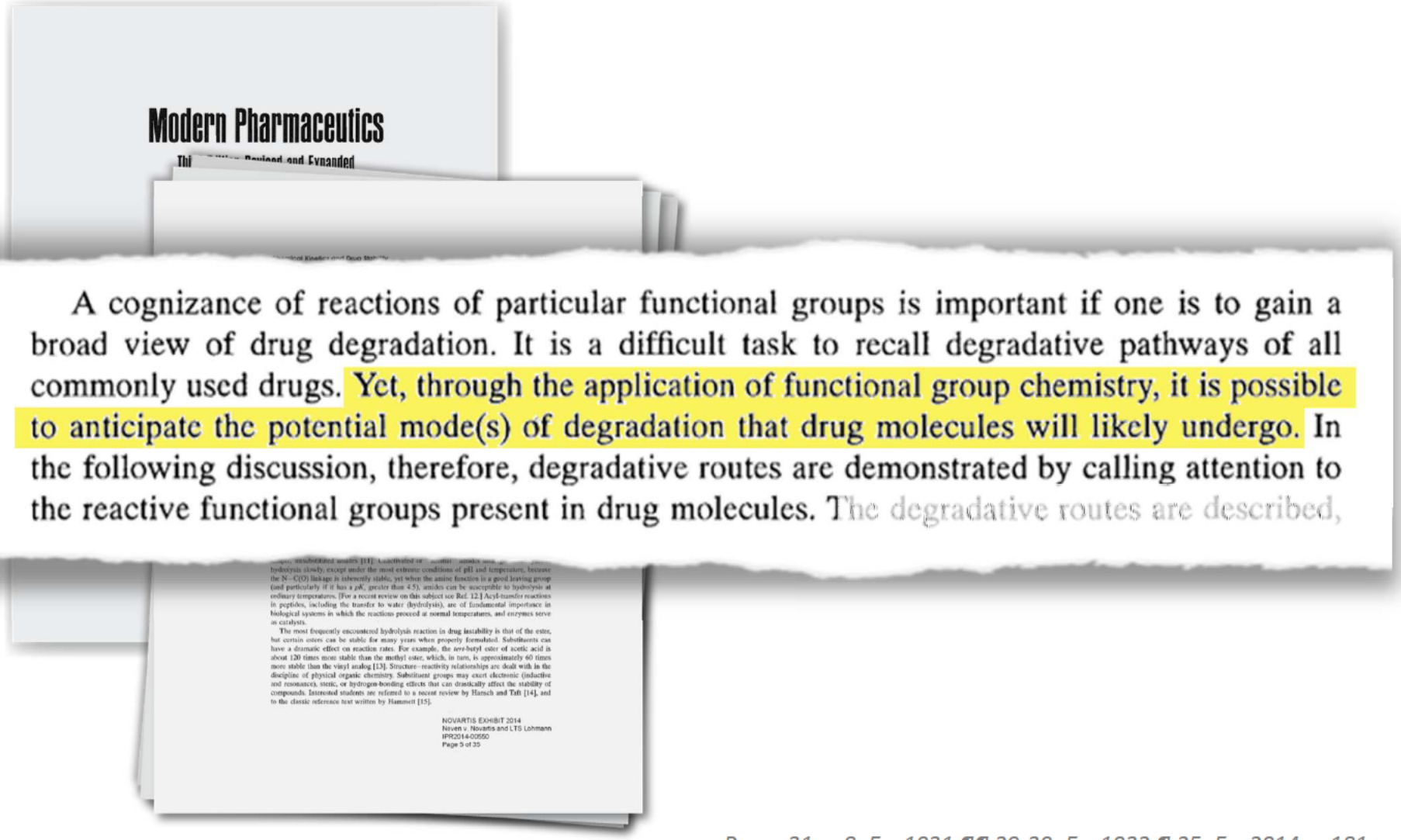
Paper 31 pp. 4-9; Ex. 1016 p. 11; Ex. 1031 ¶¶ 24-32; Ex. 1032 ¶¶ 22-26, 30-36, 52-59; Ex. 1038 p. 167; Ex. 1047 p. 46; Ex. 2014 p. 181; Ex. 2020 p. 110.

Pharmaceutical Dosage Forms and Drug Delivery Systems (Ex. 2020)



Paper 31 p. 7; Ex. 1031 ¶¶ 28, 30; Ex. 1032 ¶ 23; Ex. 2020 p. 110.

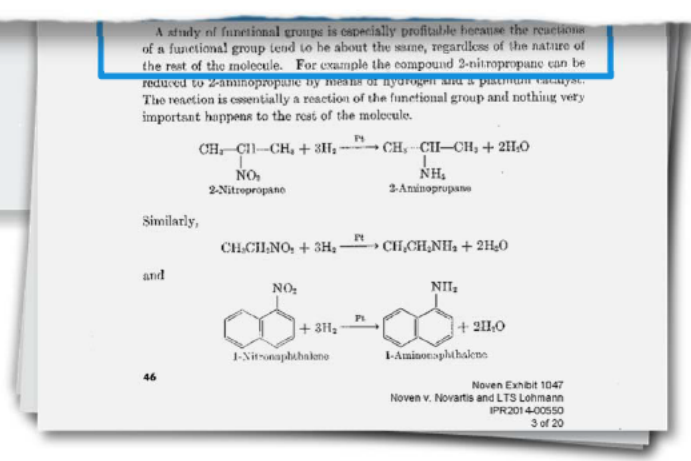
Modern Pharmaceutics (Ex. 2014)



Paper 31 p. 8; Ex. 1031 ¶¶ 29-30; Ex. 1032 ¶ 25; Ex. 2014 p. 181.

Leffler, A Short Course of Organic Chemistry (Ex. 1047)

A study of functional groups is especially profitable because the reactions of a functional group tend to be about the same, regardless of the nature of the rest of the molecule. For example the compound 2-nitropropane can be


A study of functional groups is especially profitable because the reactions of a functional group tend to be about the same, regardless of the nature of the rest of the molecule. For example the compound 2-nitropropane can be reduced to 2-aminopropane by means of hydrogen and a platinum catalyst. The reaction is essentially a reaction of the functional group and nothing very important happens to the rest of the molecule.

$$CH_3{-}CH(NO_2){-}CH_3 + 3H_2 \xrightarrow{Pt} CH_3{-}CH(NH_2){-}CH_3 + 2H_2O$$

2-Nitropropane → 2-Aminopropane

Similarly,

$$CH_3CH_2NO_2 + 3H_2 \xrightarrow{Pt} CH_3CH_2NH_2 + 2H_2O$$

and

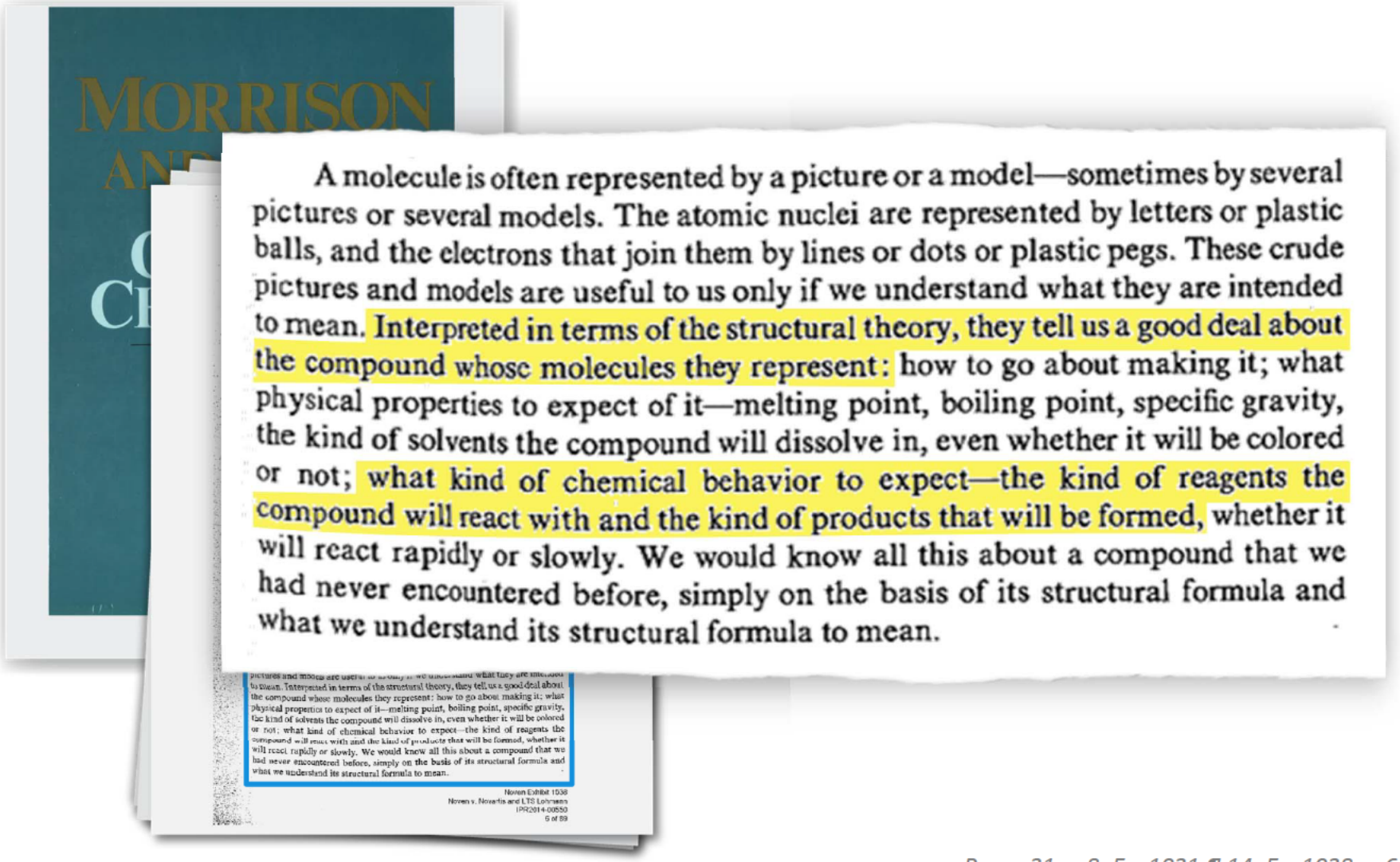
1-Nitronaphthalene → 1-Aminonaphthalene

46

Noven Exhibit 1047
Noven v. Novartis and LTS Lohmann
IPR2014-00550
3 of 20

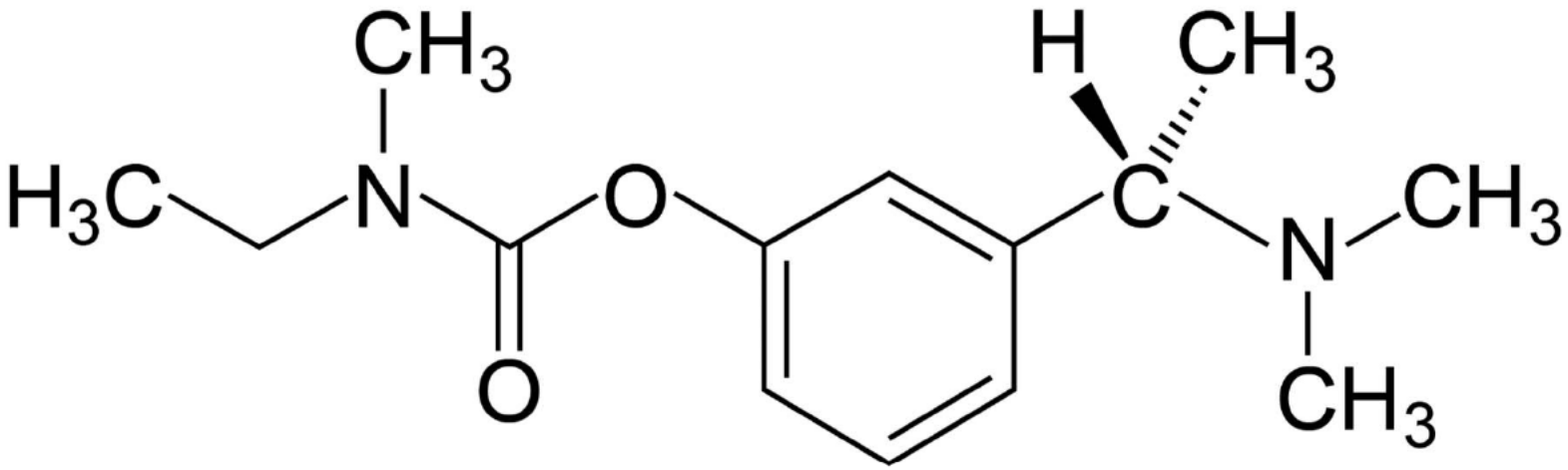
Ex. 1032 ¶ 24; Ex. 1047 p. 46.

Morrison & Boyd, Organic Chemistry (Ex. 1038)



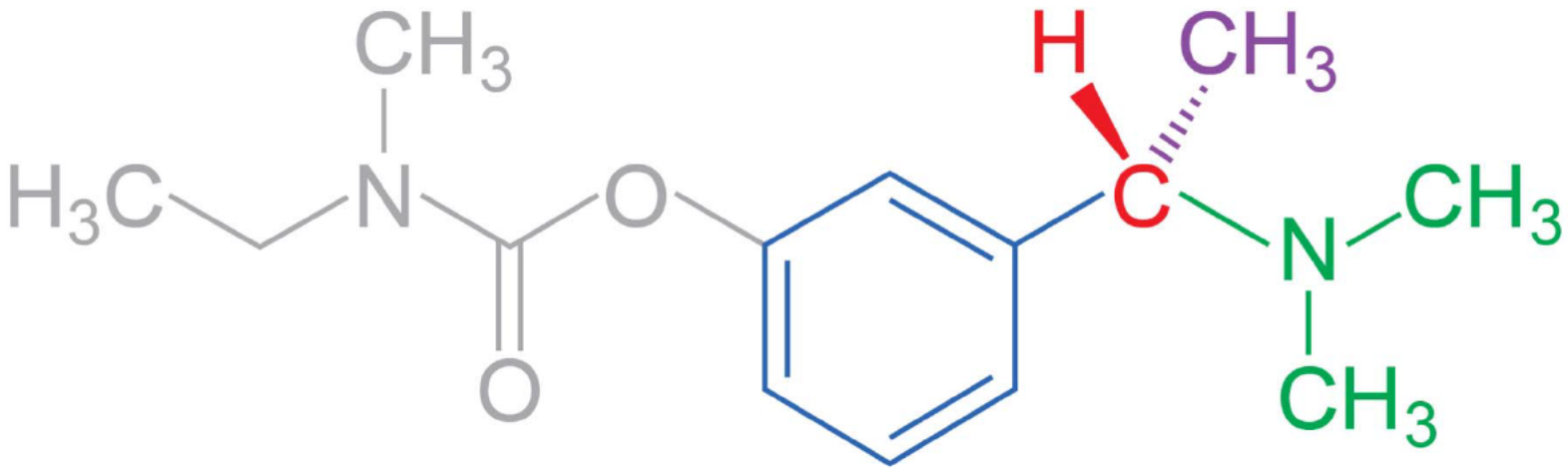
Paper 31 p. 8; Ex. 1031 ¶ 14; Ex. 1038 p. 6.

Rivastigmine



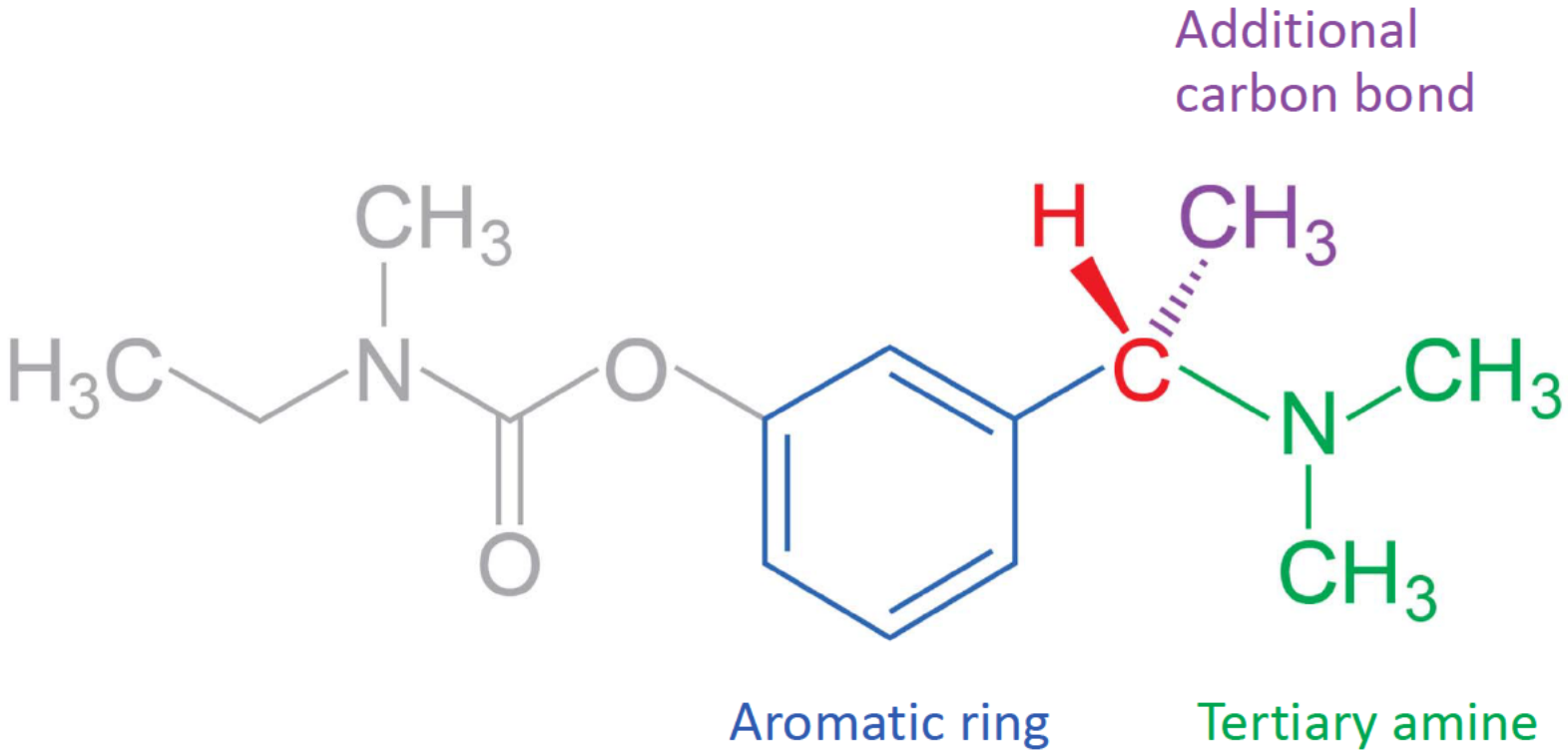
Paper 1 p. 9; Ex. 1011 ¶ 53; Ex. 1032 ¶ 14; Ex. 1002 p. 2.

Rivastigmine



Paper 1 p. 9; Ex. 1011 ¶ 53; Ex. 1032 ¶ 14; Ex. 1002 p. 2.

Rivastigmine is Susceptible to Oxidative Degradation



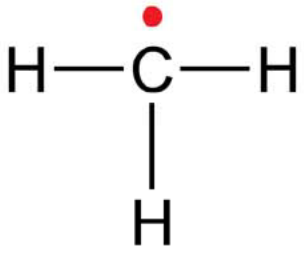
Paper 1 p. 9; Ex. 1011 ¶ 53; Ex. 1032 ¶ 14; Ex. 1002 p. 2.

Chemical Principals

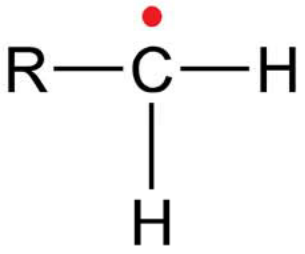
- Oxidation often involves breaking a covalent chemical bond, resulting in the formation of a radical;
- Radicals are molecules with an unpaired electron that are formed by breaking a chemical bond;
- Some chemical bonds are weaker than others depending on the structural context in the molecule (the "electronic neighborhood"), and thus are more prone to oxidation;
- A drug molecule containing a chemical bond prone to oxidation can lead to degradation of the drug.

Paper 1 pp. 34-36; Paper 31 pp. 4-5; Ex. 1011 ¶¶ 15-35, 47-49; 54-59; Ex. 1032 ¶¶ 7-15, 22-30.

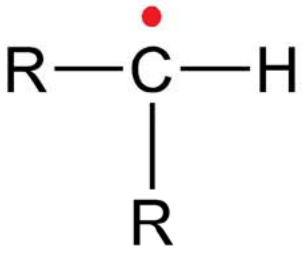
Relative Stability of Carbon Radicals



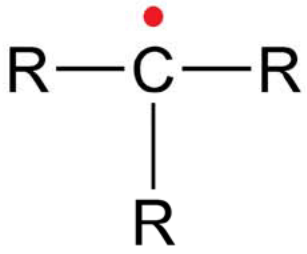
methyl
radical
(least stable)



primary
radical



secondary
radical



tertiary
radical
(most stable)

R is an alkyl group (e.g., $-CH_3$)

Ex. 1011 ¶ 20.

Carey & Sundberg, Advanced Organic Chemistry (Ex. 1007)

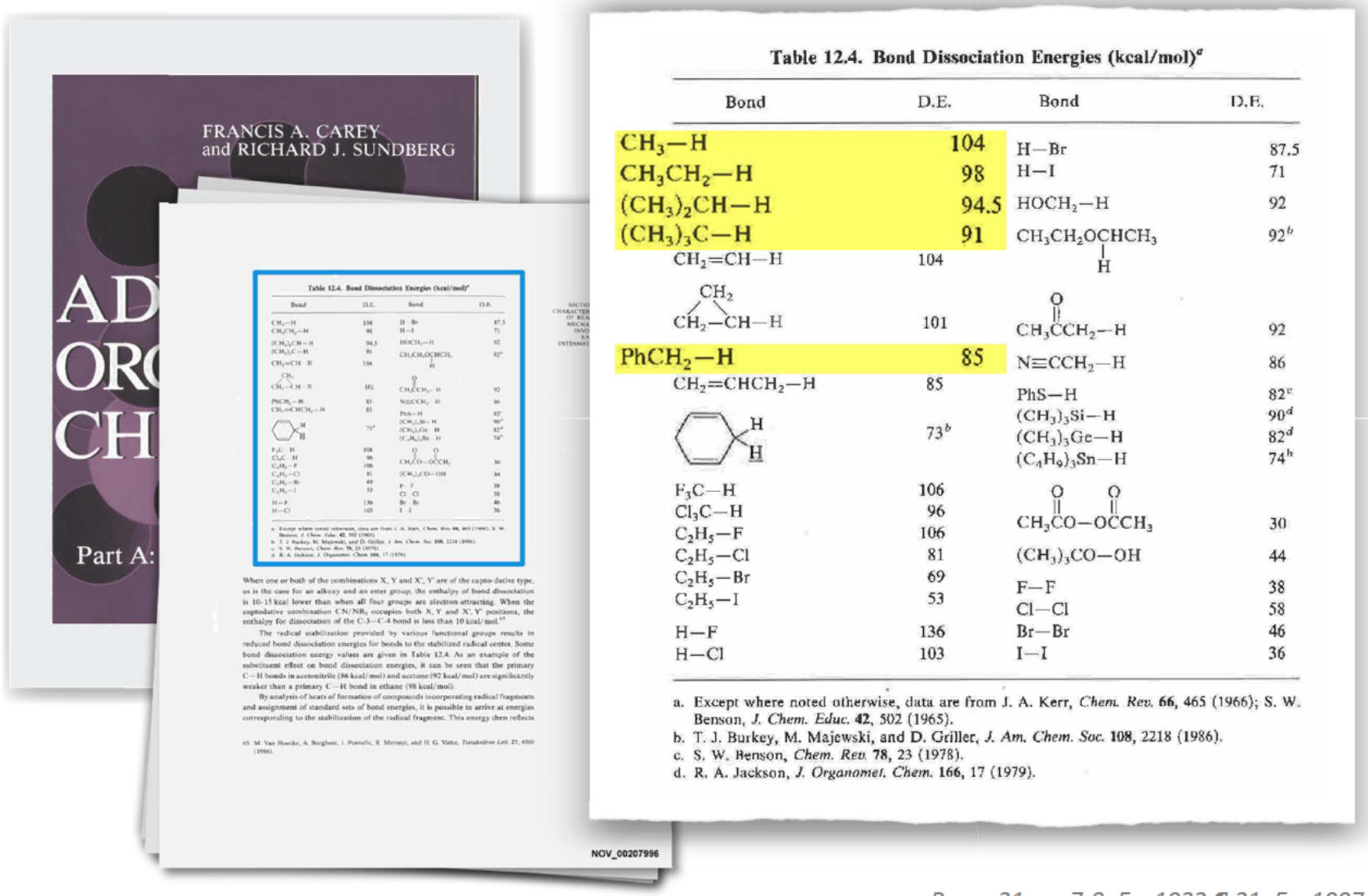


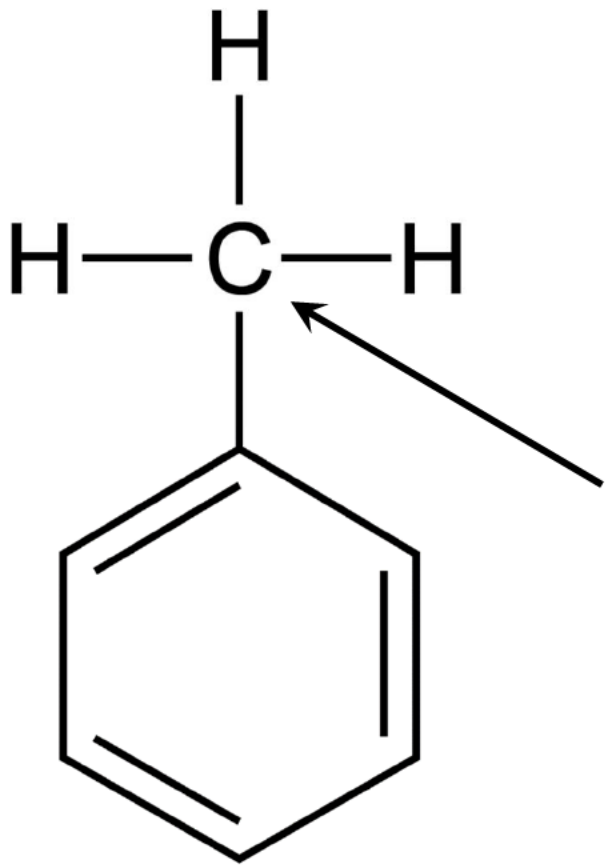
Table 12.4. Bond Dissociation Energies (kcal/mol)[a]

Bond	D.E.	Bond	D.E.
CH_3-H	104	H—Br	87.5
CH_3CH_2-H	98	H—I	71
$(CH_3)_2CH-H$	94.5	$HOCH_2-H$	92
$(CH_3)_3C-H$	91	$CH_3CH_2OCHCH_3$ (H)	92[b]
$CH_2=CH-H$	104		
	101		92
$PhCH_2-H$	85	$N\equiv CCH_2-H$	86
$CH_2=CHCH_2-H$	85	PhS—H	82[c]
	73[b]	$(CH_3)_3Si-H$	90[d]
		$(CH_3)_3Ge-H$	82[d]
		$(C_4H_9)_3Sn-H$	74[b]
F_3C-H	106		30
Cl_3C-H	96		
C_2H_5-F	106	$(CH_3)_3CO-OH$	44
C_2H_5-Cl	81	F—F	38
C_2H_5-Br	69	Cl—Cl	58
C_2H_5-I	53	Br—Br	46
H—F	136	I—I	36
H—Cl	103		

a. Except where noted otherwise, data are from J. A. Kerr, *Chem. Rev.* **66**, 465 (1966); S. W. Benson, *J. Chem. Educ.* **42**, 502 (1965).
b. T. J. Burkey, M. Majewski, and D. Griller, *J. Am. Chem. Soc.* **108**, 2218 (1986).
c. S. W. Benson, *Chem. Rev.* **78**, 23 (1978).
d. R. A. Jackson, *J. Organomet. Chem.* **166**, 17 (1979).

Paper 31 pp. 7-8; Ex. 1032 ¶ 21; Ex. 1007 p. 683.

Aromatic Rings Contribute to Radical Stability

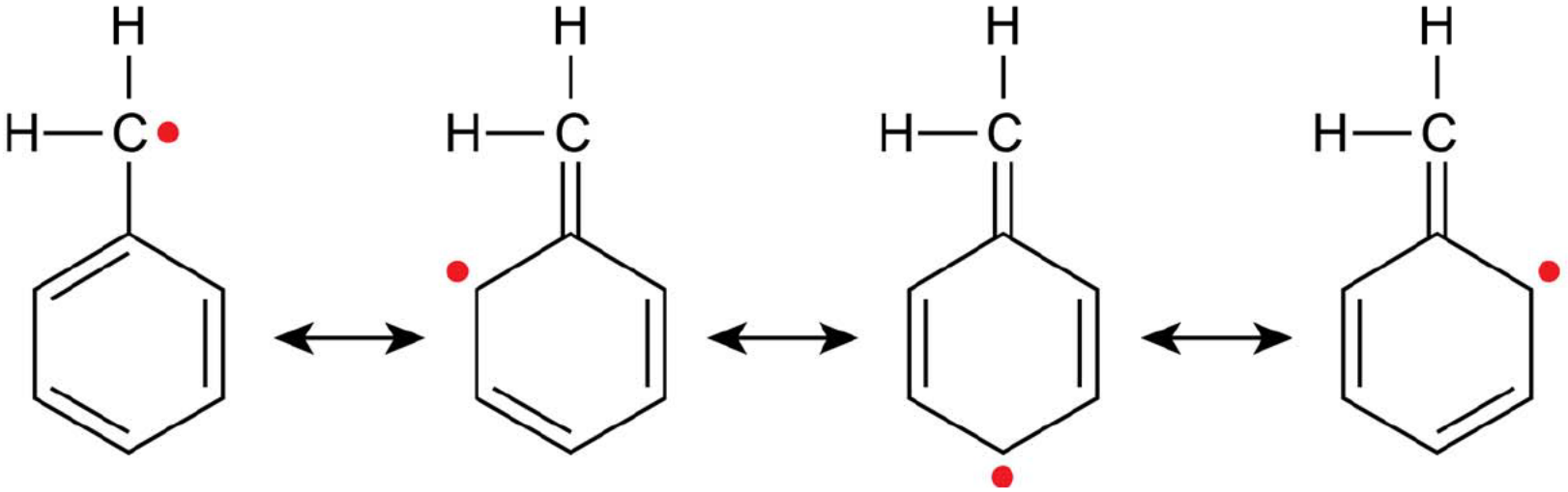


a benzylic carbon

(carbon atom adjacent to aromatic ring)

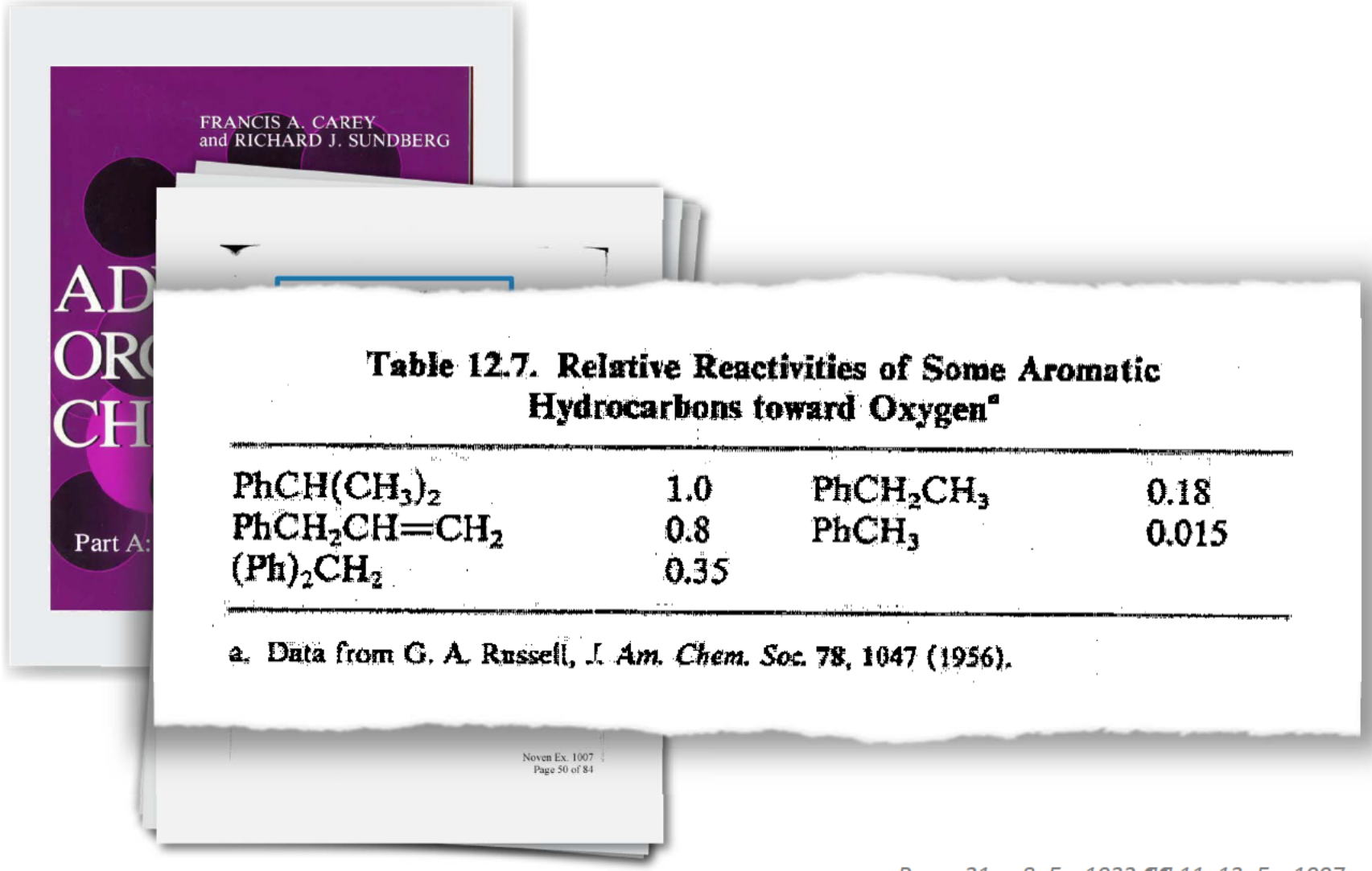
Ex. 1011 ¶ 27.

Aromatic Rings Contribute to Radical Stability by Electron Delocalization



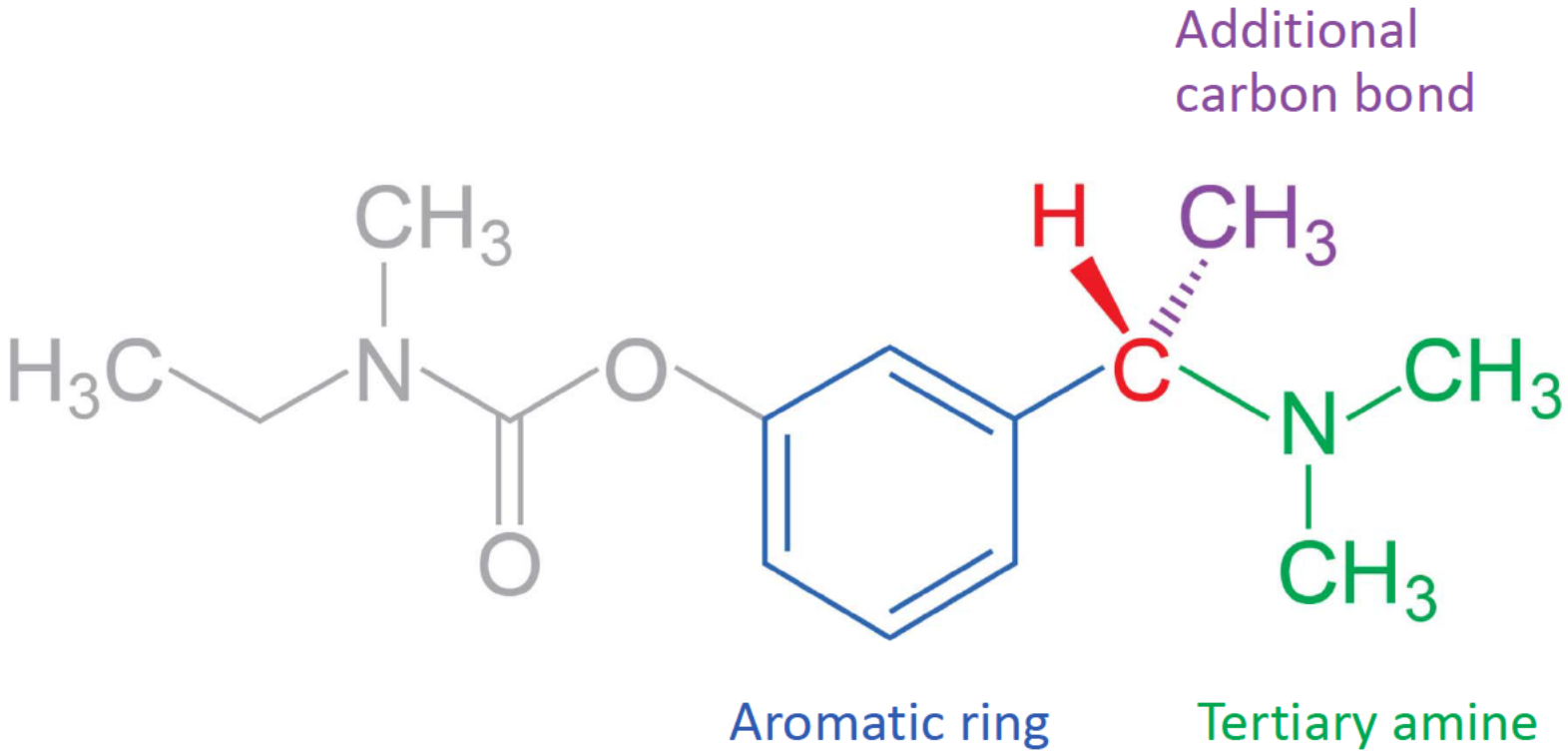
Ex. 1011 ¶ 29.

Carey & Sundberg, Advanced Organic Chemistry (Ex. 1007)



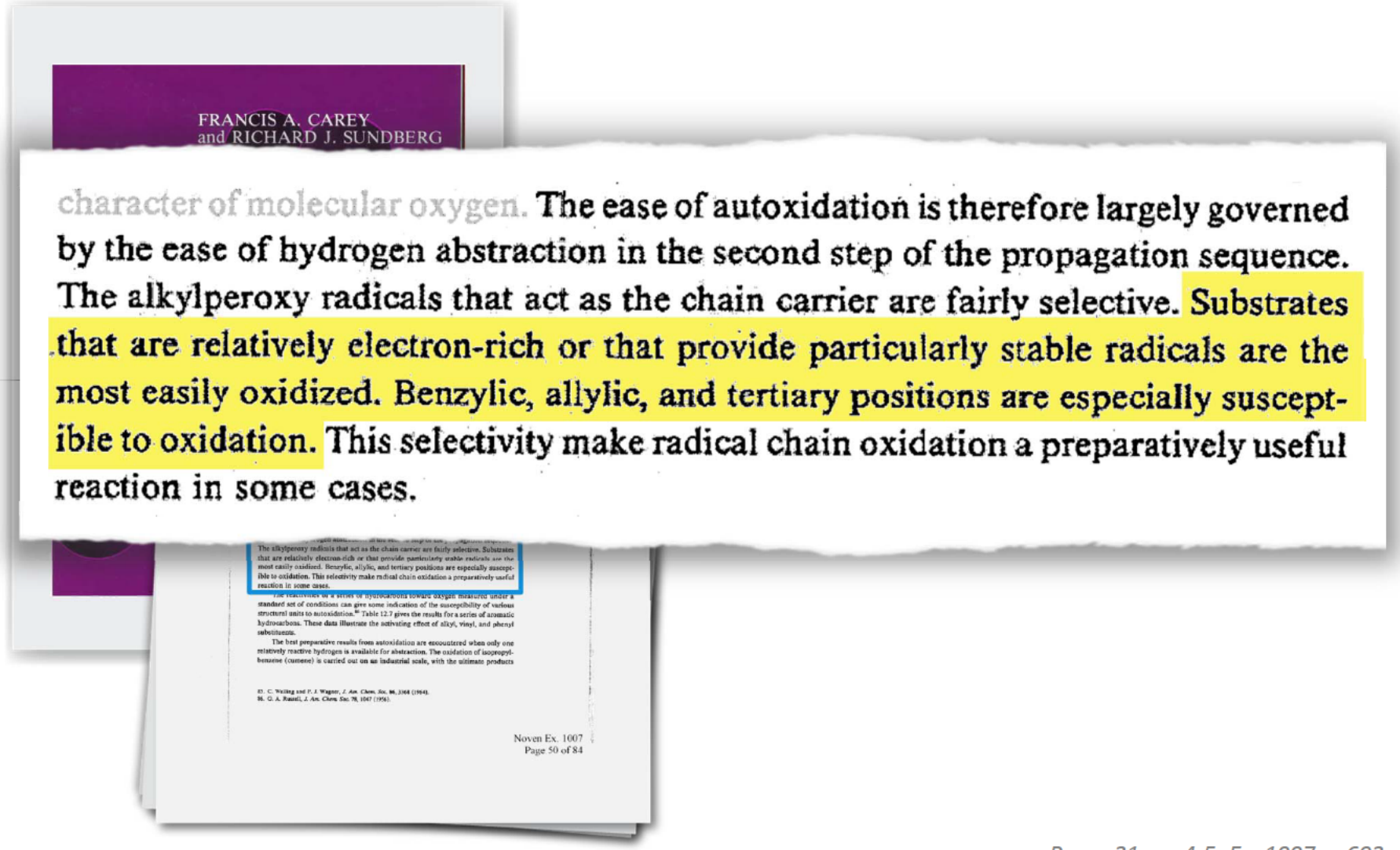
Paper 31 p. 8; Ex. 1032 ¶¶ 11, 13; Ex. 1007 p. 693.

Rivastigmine is Susceptible to Oxidative Degradation



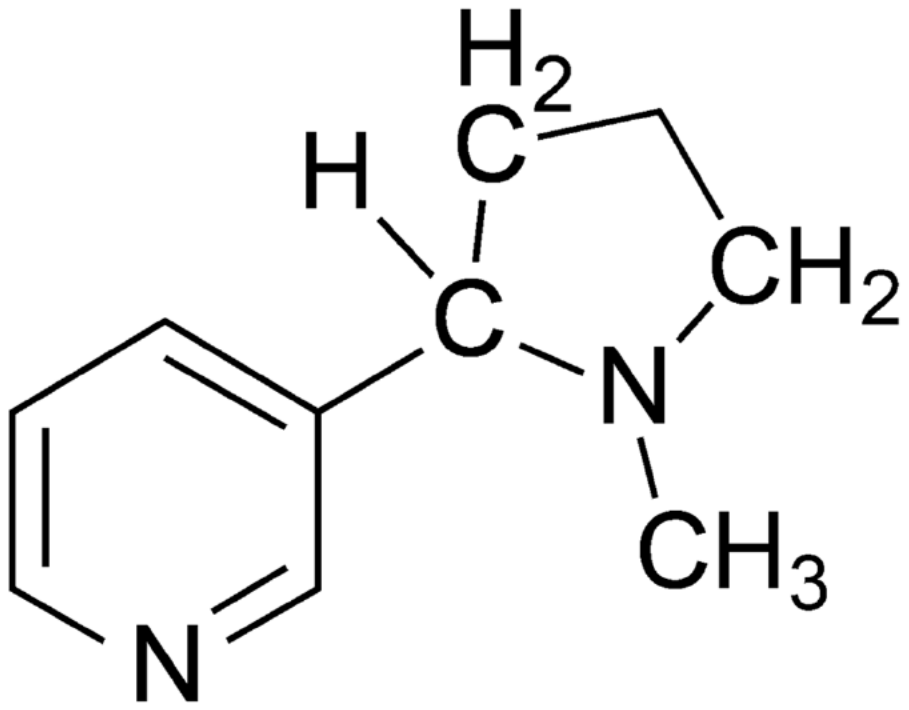
Paper 1 p. 9; Ex. 1011 ¶ 53; Ex. 1032 ¶ 14; Ex. 1002 p. 2.

Carey & Sundberg, Advanced Organic Chemistry (Ex. 1007)



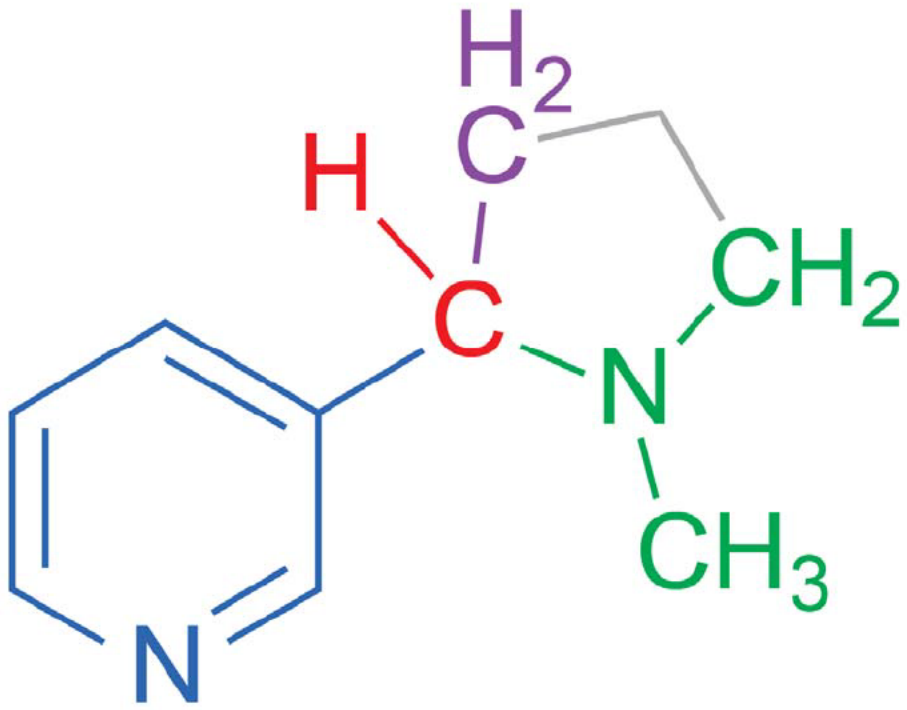
Paper 31 pp. 4-5; Ex. 1007 p. 693.

Nicotine



Paper 1 p. 14; Paper 31 pp. 5-6; Ex. 1032 ¶¶ 52-59; Ex. 1011 ¶¶ 48-49, 56-59; Ex. 1021 pp. 2-3.

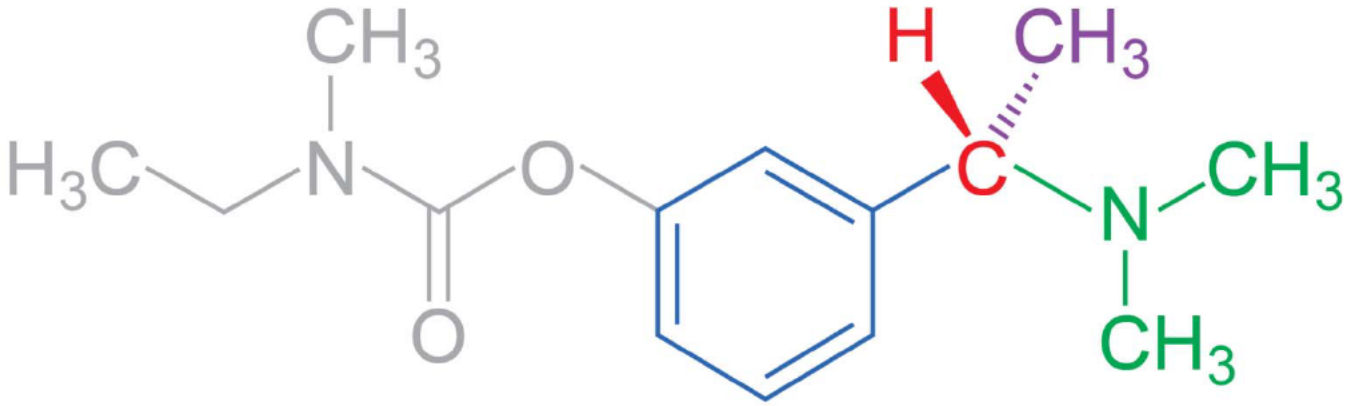
Nicotine Reinforced the POSA's Expectation of Oxidative Susceptibility



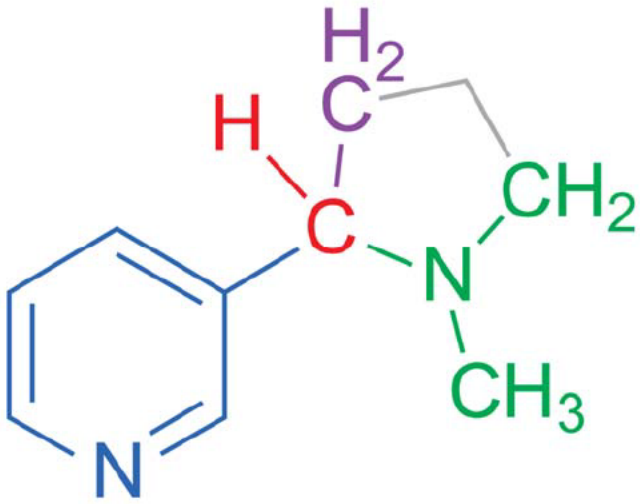
Paper 1 p. 14; Paper 31 pp. 5-6; Ex. 1032 ¶¶ 52-59; Ex. 1011 ¶¶ 48-49, 56-59; Ex. 1021 pp. 2-3.

Rivastigmine is Structurally Similar to Nicotine

Rivastigmine



Nicotine



Paper 31 pp. 5-6; Ex. 1032 ¶¶ 52-59; Ex. 1011 ¶¶ 48-49, 56-59; Ex. 1021 pp. 2-3.

The Prior Art Confirms That a POSA Would Have Maintained a Reasonable Expectation of Oxidative Instability

- The prior art instructed a POSA to make assessments about a molecule's chemical and physical properties during preformulation;
- The prior art taught that structural features affect bond strength, and in turn susceptibility to oxidation;
- The reasonable expectation is confirmed by structurally similar compounds and the prior art;
- Dr. Schöneich concluded that a POSA would have predicted rivastigmine's susceptibility to oxidative degradation based on the molecule's chemical structure.

Paper 31 pp. 4-5.

Enz

Exhibit 1002

Enz (Ex. 1002) Discloses . . .

- The structure of rivastigmine;
- A therapeutically effective amount of rivastigmine;
- How to separate rivastigmine from RA_7;
- Superiority of transdermal delivery over oral or injectable;
- Use of rivastigmine in oral, injectable, and transdermal formulations;
- An unfinished transdermal formulation containing rivastigmine, but no express inclusion of an antioxidant (Example 2).

Paper 1 pp. 13-14; Paper 31 p. 12; Ex. 1010 ¶¶ 32-35; Ex. 1002 pp. 14-15; Ex. 1031 ¶¶ 98-99.

The Handbook of Pharmaceutical Excipients

Exhibit 1003

The Handbook (Ex. 1003) Discloses . . .

- A compendium of conventional and well-characterized pharmaceutical excipients, including antioxidants;
- Many antioxidants generally regarded as safe (GRAS) and/or listed in FDA's Inactive Ingredients Guide;
- Typical antioxidant amounts used in pharmaceutical compositions, overlapping claimed amounts;
- Known incompatibilities for antioxidants;
- Respective entries for each of the antioxidants recited in dependent claims of the '023 and '031 patents.

Paper 1 pp. 17-18, 37; Paper 31 p. 15; Ex. 1003; Ex. 1010 ¶¶ 42-43, 64; Ex. 1031 ¶¶ 12, 76, 84, 86, 119, 122; Ex. 1025 147:3-148:6, 180:13-183:6; Ex. 1026 513:1-516:14.

Rosin

Ex. 1008

Rosin (Ex. 1008) Discloses . . .

- Discloses a series of compounds having greater *in vivo* activity than prior art compounds, including physostigmine;
- Experimental data for eleven RA-series compounds; most preferred compounds of the RA series: RA_4, RA_5, RA_6, **RA_7**, RA_8, RA_{14}, and RA_{15};
- Three of these RA-series compounds, including RA_7, are individually claimed;
- "Preferred antioxidants for use with the compounds of the present invention include sodium metabisulphite and ascorbic acid."

Paper 1 p. 11; Paper 31 p. 13; Ex. 1008 7:51-53, 10:9-11:16, 12:56-57, 14:11-30; Ex. 1010 ¶¶ 28-29, 59; Ex. 1031 ¶¶ 39-43.

Physostigmine vs. Rivastigmine

- The alleged teaching that rivastigmine is more stable than physostigmine only implies that rivastigmine is more stable than a very unstable compound;
  - Physostigmine is "chemically unstable";
  - Physostigmine has a very short, 20-40 minute, half-life;
  - Monomethyl derivatives, like physostigmine, "tend to be unstable in solution and hydrolyse readily at physiological pH";
- Improved *in vivo* activity is not synonymous with oxidative stability in a formulation.

Paper 1 pp. 32 n.5; Paper 31 pp. 9-10; Ex. 1008 1:30-37, 2:45-47; Ex. 1031 ¶¶ 46-48; Ex. 1026 379:16-380:5; Ex. 1026 425:6-8; Ex. 2012 ¶ 82.

Rosin (Ex. 1008)

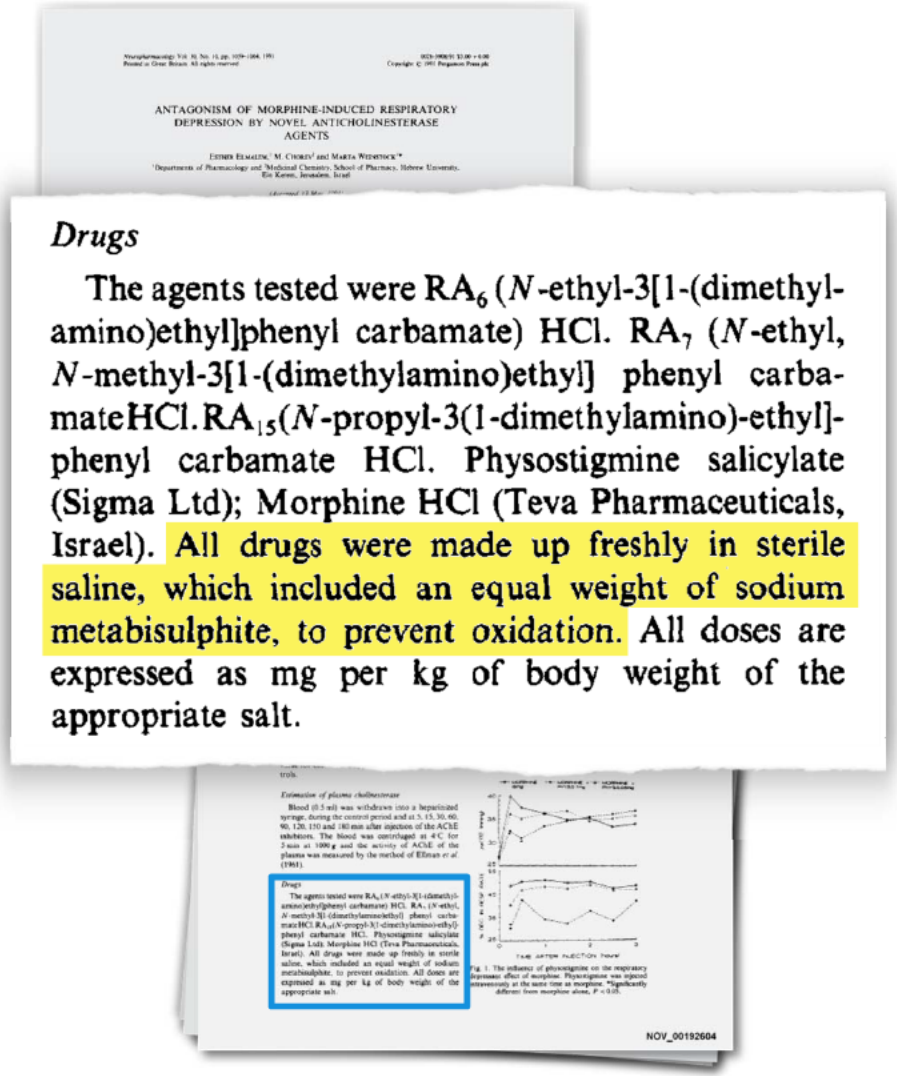
- Disclosure of preferred antioxidants for "compounds of the present invention" not limited to injectable formulations. Rosin discloses other modes of drug administration, e.g., oral, tablet, capsule;
  - Rosin discloses administration by any conventional route, which a POSA would understand to include transdermal;
- A POSA would understand that RA_7 was one of the "compounds of the present invention" and the designation of "preferred antioxidants" for compounds of the present invention connotes that work was done to arrive at that conclusion.

Paper 1 p. 33; Paper 31 p. 12; Ex. 1010 ¶ 61; Ex. 1008 7:15-19, 7:51-53, 8:56-59, 13:8-10 ; Ex. 1031 ¶¶ 38-42, 50-54.

Elmalem

Exhibit 1009

Elmalem (Ex. 1009)



ANTAGONISM OF MORPHINE-INDUCED RESPIRATORY DEPRESSION BY NOVEL ANTICHOLINESTERASE AGENTS

Drugs

The agents tested were RA_6 (*N*-ethyl-3[1-(dimethylamino)ethyl]phenyl carbamate) HCl. RA_7 (*N*-ethyl, *N*-methyl-3[1-(dimethylamino)ethyl] phenyl carbamate HCl. RA_{15} (*N*-propyl-3(1-dimethylamino)-ethyl]-phenyl carbamate HCl. Physostigmine salicylate (Sigma Ltd); Morphine HCl (Teva Pharmaceuticals, Israel). All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation. All doses are expressed as mg per kg of body weight of the appropriate salt.

NOV_00192604

- A comparative investigation of several drugs: Physostigmine vs. RA_6, RA_7, and RA_{15};
- Sodium metabisulphite antioxidant added to formulation;
- The amount of antioxidant added to RA_7 solutions is 0.3% and 0.6%.

Paper 1 pp. 12, 19; Paper 31 p. 13; Ex. 1009 pp. 1-2; Ex. 1010 ¶¶ 30, 59; Ex. 1031 ¶¶ 55, 77, 123, 134-138.

Elmalem (Ex. 1009) and Weinstock 1981 (Ex. 2046)

Elmalem (Ex. 1009)

The agents tested were RA_6 (*N*-ethyl-3[1-(dimethylamino)ethyl]phenyl carbamate) HCl. RA_7 (*N*-ethyl, *N*-methyl-3[1-(dimethylamino)ethyl] phenyl carbamate HCl. RA_{15} (*N*-propyl-3(1-dimethylamino)-ethyl]-phenyl carbamate HCl. Physostigmine salicylate (Sigma Ltd); Morphine HCl (Teva Pharmaceuticals, Israel). All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation. All doses are expressed as mg per kg of body weight of the appropriate salt.

Weinstock 1981 (Ex. 2046)

(1961). Drugs used were: ATMN, hyoscine hydrobromide, neostigmine hydrobromide and physostigmine salicylate (Sigma Chemical Company, St. Louis, MO); morphine hydrochloride (U.S. Vitamins Laboratories Division, Tuckahoe, NY); and naloxone hydrochloride (Endo Laboratories, Inc., Garden City, NY). Morphine and physostigmine were made up freshly for each experiment in sterile saline which included an equal weight of ascorbic acid to prevent oxidation. All doses are expressed in milligrams per kilogram of body weight of the appropriate salt.

Ex. 1031 ¶¶ 59-60; Ex. 1009 p. 2; Ex. 2046 p. 2.

Elmalem Did Not Use Antioxidants Indiscriminately

Year	Reference	Antioxidant
1991	Ex. 1009: Elmalem	Morphine: YES (sodium metabisulphite) Physostigmine: YES RA_6: YES RA_7: YES RA_{15}: YES
1981	Ex. 2046: Weinstock 1981	Morphine: YES (ascorbic acid) Physostigmine: YES Neostigmine: NO Naloxone: NO ATMN: NO Hyoscine: NO

Ex. 1031 ¶¶ 57-59; Ex. 1009 p. 1; Ex. 2046 p. 2.

Elmalem (Ex. 1009)

- Elmalem unambiguously discloses that an antioxidant is added "to prevent oxidation";
- The amount of antioxidant used is within the Handbook range;
- It is undisputed that RA_7 and rivastigmine behave the same with respect to oxidation.

Paper 1 pp. 19, 42; Paper 31 p. 13; Ex. 1031 ¶¶ 57, 61-63, 77, 104-105; Ex. 2012 ¶ 96 n.8.

Ebert

Exhibit 1006

Ebert (Ex. 1006) Discloses . . .

- Transdermal system with nicotine and antioxidants;
- Nicotine oxidizes when exposed to air;
- Antioxidant use is a solution to oxidative degradation in a transdermal patch;
- Antioxidants include BHT, BHA, and α-tocopherol;
- Most preferred weight percentage of BHT is 0.05 to 0.2 weight percentage of nicotine;
- Applicable to "any other liquid drug" that can be transdermally administered.

Paper 1 pp. 14-16; Paper 31 p. 12; Ex. 1010 ¶¶ 36-39; Ex. 1031 ¶¶ 108-109; Ex. 1006 13:33-36.

Ebert (Ex. 1006)

- Ebert discloses controlling oxidation of nicotine even during the short duration of the manufacture of a transdermal formulation, which a POSA would find relevant to stabilizing a rivastigmine formulation during a multi-year shelf life;
- A POSA would understand that Ebert is not limited to a particular manufacturing method; other liquid drugs, regardless of volatility, can be substituted.

Paper 1 p. 16; Paper 31 p. 12; Ex. 1010 ¶ 39; Ex. 1031 ¶¶ 106-110; Ex. 1006 pp. 3, 5, 13.

Sasaki

Ex. 1005

Sasaki (Ex. 1005) Discloses . . .

- Broad range of amine-containing compounds (like rivastigmine) will often degrade when combined with an acrylic adhesive;
- Oxidative degradation not prevented by oxygen-impervious packaging;
- Oxidative degradation prevented by antioxidant, (tocopherol; 0.022 to 0.44% weight percent);
- Three-month stability study of amine-containing compounds combined with an acrylic adhesive, with and without antioxidant.

Paper 1 pp. 16-17, 46-47; Paper 31 pp. 13-14; Ex. 1010 ¶¶ 40-41, 84-87; Ex. 1031 ¶¶ 79-82; Ex. 1025 160:8-166:1, 189:12-193:16, 198:14-199:18.

Enz (Ex. 1002) & Sasaki (Ex. 1005)

- Enz discloses a **transdermal** device and formulation of the **amine-containing** compound rivastigmine combined with an **acrylic** adhesive;
- Sasaki discloses that **amine-containing** compounds will degrade when combined with an **acrylic** adhesive in a **transdermal** device, and teaches that an antioxidant prevents this degradation.

Paper 1 pp. 46-47; Ex. 1010 ¶¶ 85-86; Ex. 1031 ¶ 89; Ex. 1025 199:19-200:10.

Addressing Patent Owners' Arguments

- The expectation that rivastigmine would be susceptible to oxidative degradation is not unreasonable;
- The prior art did not teach that rivastigmine was stable;
- A POSA would have been motivated to combine the teachings of the prior art to arrive at the claimed invention;
- The prior art did not discourage the use of an antioxidant.

Paper 31 pp. 4-15.

The Expectation of Susceptibility to Oxidative Degradation is Not Unreasonable

- A POSA assessed the stability of a drug molecule under pharmaceutically-relevant conditions applying functional-group chemistry;
- No dispute that the particular structural features of rivastigmine result in a weakened C-H bond;
- The prior art is consistent with the POSA's expectation that the rivastigmine molecule is susceptible to oxidative degradation:
  - Elmalem discloses the use of antioxidant with RA_7 to prevent oxidation;
  - Rosin discloses the use of antioxidant with RA_7, among others, as required;
  - Ebert discloses the use of antioxidant with transdermally-delivered nicotine.

Paper 31 pp. 4-5, 7-8, 13; Ex. 1032 ¶¶ 14, 18-19, 30-36; Ex. 1008, 7:48-53; Ex. 1009 p. 1060; Ex. 1006, 19:17-33.

The Expectation of Susceptibility to Oxidative Degradation is Not Unreasonable

- A POSA would have been aware that rivastigmine is particularly susceptible to oxidative degradation;
- The POSA would not have been surprised to observe oxidative degradation;
- A POSA would conduct testing to confirm the extent of oxidative degradation in a particular formulation.

Paper 31 pp. 6-8; Ex. 1032 ¶¶ 15, 22-26, 30-36; Ex. 1031 ¶¶ 10, 25, 28-37, 92; Ex. 1048 91:15-92:15.

The Prior Art Does Not Teach That Rivastigmine is Oxidatively Stable

- The prior art discloses use of antioxidant with RA_7;
- The prior art comparison of rivastigmine with physostigmine does not teach that rivastigmine is oxidatively stable;
- Commercial formulations containing a drug otherwise having the same structural features as rivastigmine giving rise to susceptibility to oxidation, but not reporting an antioxidant, do not demonstrate that a molecule's structure has no predictive value.

Paper 31 pp. 9-10; Ex. 1032 ¶¶ 37-40, 41-51, 57.

Alleged "Real World" Examples are Irrelevant

***Novartis v. Noven,* Cross-Examination of Dr. Klibanov:**

Q. Will you agree with me that a commercial product that does not list an antioxidant among its ingredients does not necessarily tell you that the API, the active drug is not subject to oxidative degradation?

A. Yes, I agree with that.

Ex. 1026 553:1-6; Ex. 1031 ¶ 90.

Motivation to Add an Antioxidant

- Chemical structure of rivastigmine indicated susceptibility to oxidative degradation;
- Analogous structure to nicotine, which was known to be susceptible to oxidation;
- Prior art, including Elmalem, Rosin, Sasaki, Ebert, and Enz, was consistent with POSA's expectations;
- No dispute that antioxidants were conventionally employed to address oxidative degradation issues in pharmaceutical compositions;
- Prior art use of antioxidants and Handbook provide the POSA with an expectation of compatibility and successful formulation.

Paper 1 pp. 17-18, 34-37, 47; Paper 31 pp. 4-6, 10-15; Ex. 1011 ¶¶ 50-59; Ex. 1010 ¶¶ 30-31, 35, 38, 51, 84; Ex. 1031 ¶¶ 37-40, 57, 84-86, 88-89, 92, 109, 116-23.

The Prior Art Did Not Discourage the Use of an Antioxidant

- Numerous antioxidants were classified by the FDA as Generally Recognized as Safe (GRAS);
- Several antioxidants (sodium metabisulfite, ascorbic acid) were known to be compatible with rivastigmine;
- Other means of preventing oxidation were understood to be sometimes difficult to employ;
- It would have been routine work for a POSA to select an effective amount of an appropriate antioxidant;
- Prior art may counsel judicious use, but not discourage use.

Paper 31 pp. 14-15; Ex. 1031 ¶¶ 12, 76, 84, 90, 93, 116-123; Ex. 1003 pp. 5-22; Ex. 1008 7:51-53; Ex. 1009 p. 1060; Ex. 2019 p. 2/4.

Duration of Action *in vivo* is Not Oxidative Stability

- "Greater" stability than the very unstable physostigmine is not significant, and also…
- Rosin, Weinstock 1986, Enz 1991, Weinstock 1994 refer to *in vivo* activity of rivastigmine, not stability in pharmaceutical compositions:
  - Rosin (Ex. 1008): four possible reasons (*e.g.*, metabolism, lipid solubility) for greater activity in the body;
  - Weinstock 1986 (Ex. 2036): greater in vivo activity, same four possible reasons as stated in Rosin;
  - Enz 1991 (Ex. 2026): longer duration of action;
  - Weinstock 1994 (Ex. 2027): duration of action in animals and humans.

Paper 31 p. 10; Ex. 1031 ¶¶ 46, 68-70; Ex. 1008 11:22-25, 11:29-35; Ex. 2036 p. 546; Ex. 2026 p. 272; Ex. 2027 p. 219.

Petitioner's Motion to Exclude: Exhibits

- Ex. 2015: Compilation of two Patent Owner internal documents;
- Ex. 2032: Compilation of three Patent Owner internal documents;
- Ex. 2053: Selected portions of Dr. Tiemessen' testimony from the *Novartis v. Watson* trial;
- Ex. 2061: Ex. 2053 with additional pages of testimony added, first introduced at Dr. Kydonieus' April 20, 2015 deposition;
- Ex. 2059: One-page excerpt of internal Novartis document, first introduced at Dr. Schöneich's April 18, 2015 deposition;
- Ex. 2062: Ex. 2059 with the additional 29 pages of the underlying document that were originally omitted, filed May 12, 2015.

Paper 47, 57.

CERTIFICATE OF SERVICE

I certify that, on May 26, 2015, the foregoing PETITIONERS' DEMONSTRATIVES was served electronically on Patent Owners and Mylan using the following email addresses:

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