

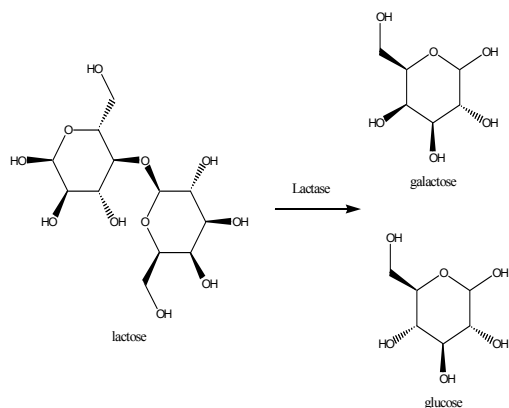
Passage I (Questions 1-4)

Cow's milk is a nutritionally complete food source which contains water, vitamins, minerals, proteins, carbohydrates, and lipids.

An important protein in milk is *casein*. This typically exists in milk as its calcium salt, *calcium caseinate*. Calcium caseinate is soluble at the normal pH of milk (6.6), but it becomes an insoluble form of casein in solutions that have a lower pH of 4.6 (the isoelectric point of calcium caseinate).

Milk contains two other important types of proteins, which can be denatured and precipitated by heat, namely *lactalbumins* and *lactoglobulins*.

Lactose (shown below), is the main carbohydrate in milk. It is a disaccharide which can be hydrolyzed with acid to give two monosaccharides, galactose and glucose. In the body, the enzyme *lactase*, digests lactose to galactose and glucose.



Adding a dilute solution of acetic acid to nonfat milk is the first step in isolating several of the components of milk. The solid material that precipitates (Solid 1) is removed. Care must be taken to avoid adding an excess of acetic acid.

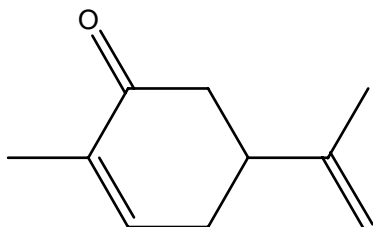
The remaining acidic solution is then treated with powdered CaCO_3 and heated to boiling, after which time another solid (Solid 2) forms. Solid 2 is removed by filtration, and hot ethanol is added to the aqueous filtrate. The solution is

allowed to cool overnight, during which time lactose crystallizes in the flask.

1. A) The passage states that an insoluble form of casein forms as the pH decreases from 6.6 to 4.6. Sour milk is acidic.
2. A) The passage describes three specific types of compounds: (1) Calcium caseinate, which precipitates at low pH as casein; (2) Proteins (lactalbumins and lactoglobulins), which precipitate when denatured by heat; and (3) Lactose, which hydrolyzes to galactose and glucose. In the method mentioned in the passage, the powdered calcium carbonate is probably added to neutralize any remaining acetic acid. Solid 1 (casein) forms on the addition of acetic acid and is removed by filtration, so it is not present when the CaCO_3 is added. Solid 2 (denatured and precipitated proteinaceous material) is insoluble in the CaCO_3 .
3. C) H_2O
From the equation it can be seen that the hydrolysis of lactose results in the net addition of H_2O during the cleavage of the disaccharide.
4. C) Solid 2 forms after the solution is heated to boiling, a condition that denatures and precipitates the lactalbumins and lactoglobulins

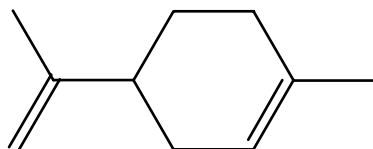
Passage II (Questions 5-9)

Carvone (shown below) can exist as one of two enantiomers. One of them, (-)-carvone is responsible for the fragrance of spearmint oil and the other, (+)-carvone, provides the characteristic odor in caraway seed oil.



carvone

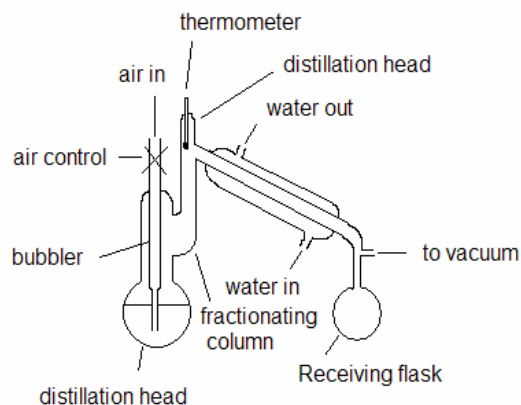
A chemist attempted to isolate (+)-carvone from caraway seed oil, which consists almost entirely of (+)-carvone and limonene (shown below).



limonene

Because the two compounds have different boiling points, *vacuum fractional distillation* was chosen as the method of separation. The apparatus in Figure 1 was assembled, and a sample of caraway seed oil was placed in the distillation flask. A bubbler (or ebulliator) was lowered into the distillation flask to introduce small air bubbles into the system. The fractionating column and distillation head were wrapped with glass wool, and the apparatus was connected with thick tubing to a vacuum source. The contents of the distillation flask were heated,

and two fractions were collected in the receiving flask.

**Figure 1** Vacuum distillation apparatus

- The carbonyl group (C=O) in carvone makes it more polar and it thus has a higher boiling point (due to non-bonding interactions) than the hydrocarbon limonene (which contains no polar groups).
- C) The passage mentions that the bubbler (ebulliator) was added to introduce small air bubbles into the system. This is the same function provided by a boiling chip at atmospheric pressure. The air bubbles prevent superheating and bumping.
- A) The separation of limonene and (+)-carvone can be improved by modifying either the apparatus shown in Figure 1 or the method. The separation of the two liquids takes place in the fractionating column as the two liquids vaporize and condense, the lower-boiling liquid distilling first. If the fractionating column is shortened (Answer D), the liquids will vaporize and condense fewer times (i.e. there will

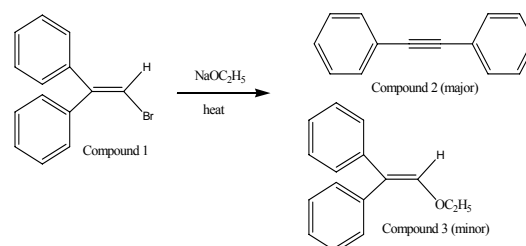
be fewer theoretical plates) and the level of separation will not be as effective. Cooling the condenser with ice water (Answer C) will have no effect on the degree of separation because condensation takes place after the separation has occurred. Creating a lower pressure inside the distilling apparatus (Answer B) will lower the boiling points of both liquids and reduce the differences in boiling point making it more difficult to effect a separation of the two compounds. Heating the distillation flask at a slower rate (Answer A) will allow both liquids more time in the fractionating column (increase the number of theoretical plates, allowing liquid and vapor to equilibrate) and therefore effect a greater degree of separation of the two compounds.

8. B) Carbon 5 is the only stereogenic carbon atom (chiral center, carbon attached to 4 different functional groups); carbons 2 and 7 are not stereocenters.
9. A) The boiling point of a liquid is the temperature at which the vapour pressure of the liquid equals the surface pressure. The vapor pressure of a liquid increases with increasing temperature. Hence, the boiling point of a liquid decreases as the pressure on the surface of the liquid is decreased (with applied vacuum). If a leak develops in the apparatus, the vacuum will decrease and the surface pressure will increase, as will the boiling points of both liquids.

Passage III (Questions 10-14)

When Compound 1 is heated with NaOEt, Compounds 2 and 3 are formed

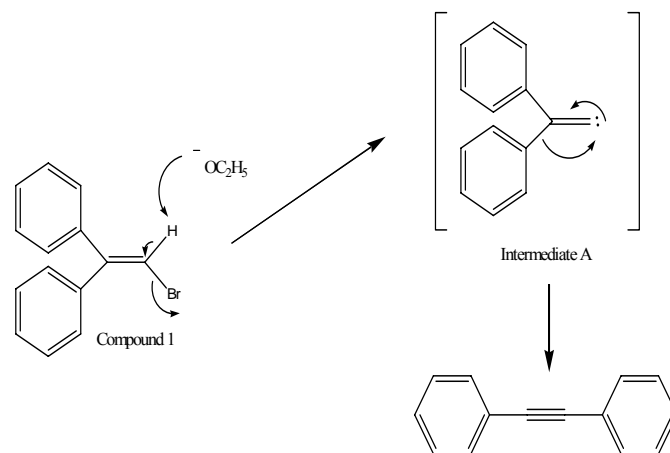
(Reaction 1).



Two mechanisms were proposed for Reaction 1.

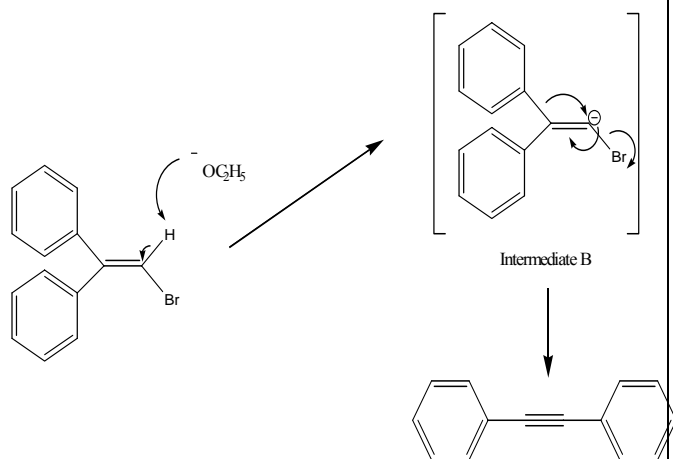
Mechanism A

HBr is eliminated from Compound 1 to form a symmetrical vinyl *carbene*, Intermediate A, which then rearranges to form Compound 2.

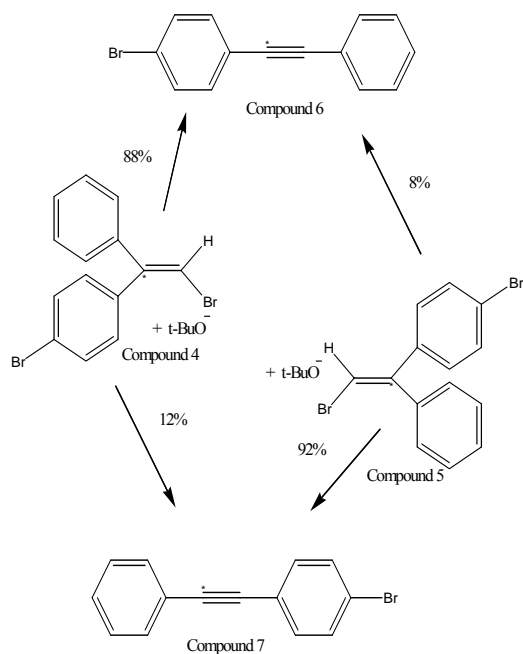


Mechanism B

Ethoxide abstracts a proton from Compound 1 to produce a carbanion, Intermediate B. This then rearranges, with loss of bromide, to form Compound 2.



To distinguish between the 2 mechanisms, an isotopic labeling experiment was designed. 2 compounds (Compounds 4 and 5) were labeled with carbon-14 (^{14}C), and then each was treated with potassium *t*-butoxide (see Scheme 1). Because Compounds 4 and 5 formed varying ratios of Compounds 6 and 7, Mechanism A was ruled out.



Scheme 1 (* denotes C^{14} label)

10. C) If a carbene was the intermediate (intermediate A), then Compound 4 and Compound 5 would form identical intermediates that would go on to yield equal amounts of compounds 6 and 7.

11. B) As seen in Reaction 1, OCH_2CH_3 replaces Br in a substitution reaction.

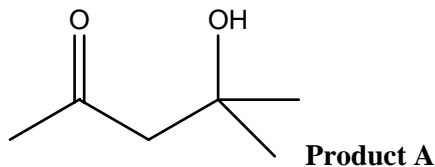
12. A) By either mechanism, ethoxide abstracts a proton to form ethanol, EtOH , and a bromide ion is liberated. The Na^+ (from NaOEt), joins with the Br^- to form NaBr

13. D) Neither Compound 2 nor Compound 6 is optically active; therefore, the specific rotation of both compounds is zero

14. A) Compound 1 contains only sp^2 hybridized carbon atoms. Compound 2 only contains sp and sp^2 hybridized carbon atoms. The carbon-carbon double bond that is not part of the two benzene rings in Compound 1 contains sp^2 hybrid orbitals. This double bond undergoes transformation in Reaction 1 resulting in a carbon-carbon triple bond in Compound 2. The carbons of the carbon-carbon triple bond contains sp hybrid orbitals.

Passage IV (Questions 15-20)

As part of an experiment, a starting material was treated with NaOH in acetone solvent ($(\text{CH}_3)_2\text{C}=\text{O}$) however, the starting material was recovered unreacted. Instead a small amount of Product A (shown below) was isolated.



It was determined that Product A resulted from the aldol self-condensation of acetone. Product A was identified based on the following observations.

Observations about Product A

- Product A had a molecular weight of 116.
- Elemental analysis of Product A showed only carbon, hydrogen, and oxygen in the molecule.
- Signals in the infrared spectrum of Product A included a broad band at 3400 cm^{-1} and an intense signal at 1720 cm^{-1} .
- Product A was a methyl ketone as it gave a positive iodoform test.
- When Product A was treated with Br_2 in CCl_4 , the red bromine colour persisted, because no carbon-carbon double bonds were present to react with the bromine.

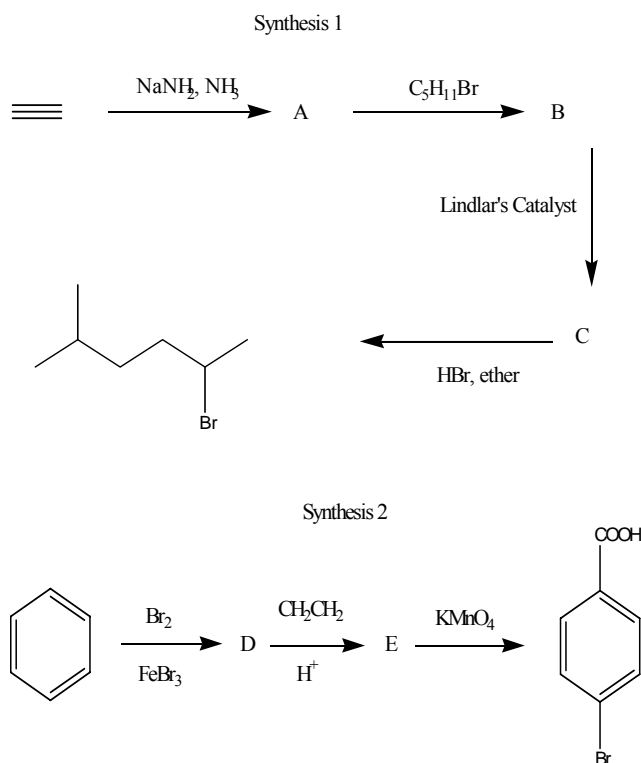
The structure of Product A was further confirmed when treatment with hot sulfuric acid resulted in the corresponding dehydration product, Product B.

- B) The question states that the product of the aldol self-condensation is a β -hydroxy ketone, meaning that the condensation is not complete, in that the product has not lost water. (Note: An aldol addition reaction forms a β -hydroxycarbonyl compound; whereas, an aldol condensation reaction implies that the addition product has lost water.) Because the addition product is a dimer of the starting compound, the product has a molar mass that is twice that of the starting compound. Thus the molecular weight of the starting compound is $144/2 = 72$.
- C) This question involves a reaction at equilibrium. Thus, Le Châtelier's principle is in effect, and the position of equilibrium can be shifted toward Product A by removing it as it forms. Catalysts (Answers A and B) do not affect the position of equilibrium, and heating acetone to the boiling point (Answer D) would remove reactant and shift the equilibrium to the left.
- D) is a constitutional isomer of Product A; the other compounds are not.
- B) Product B contains a double bond, because it results from the dehydration (loss of a molecule of water) of Product A. Thus, the addition of a drop of Br_2/CCl_4 to Product B will result in the red color of bromine disappearing as bromine adds across the double bond.
- A) The six hydrogen atoms in acetone are magnetically equivalent and their ^1H NMR signal appears as a singlet near $\delta = 2$ ppm.

20. D) All three compounds are methyl ketones. The passage states that Product A gives a positive iodoform test, so we can deduce that all three compounds give a positive iodoform test.

Passage V (Questions 21-25)

A chemist wishes to make the products shown below by the following synthetic schemes.



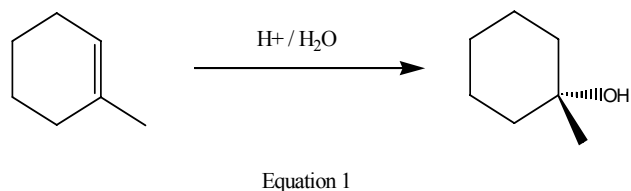
21. D) Acetylene has an acidic H atom which can be removed by the NaNH_2 base to give acetylide anion.
22. B) Acetylide anion performs an $\text{S}_{\text{N}}2$ attack on the alkylhalide to give 5-methyl-hept-1-yne. Looking at the final product gives the structure of the alkyl component.
23. B) Lindlars catalyst reduces the alkyne to an alkene

24. C) The conditions employed effect an electrophilic aromatic substitution reaction, a bromination of benzene.

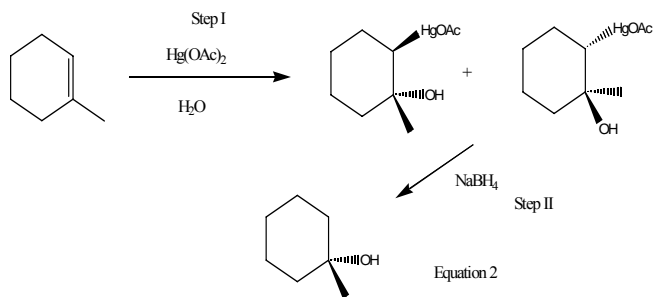
25. A) The conditions employed create a carbocation from H^+ addition to ethene. The carbocation then effects an EAS reaction in a similar fashion to a Friedel Crafts alkylation at a position para to the bromine atom (bromine is an o,p-director).

Passage VI (Questions 26 - 29)

Three different methods of preparing alcohols from alkenes are shown below:

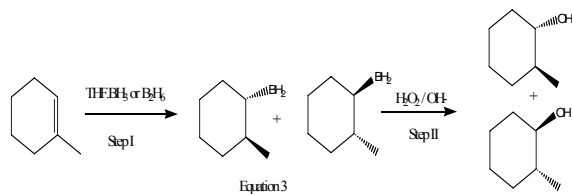


Equation 1 shows the acid catalysed hydration of an alkene. The reaction is regioselective and not stereoselective and rearrangements may occur.



Equation 2 shows the oxymercuration/demercuration reaction. This is a two step reaction and the final alcohol is formed via the oxymercuration alcohols shown after step I. The mercury is then removed in the second step by NaBH_4

to give the alcohol product. Overall the reaction is regioselective and the first step is also stereoselective and no molecular rearrangements occur.



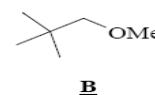
Equation 3 shows a hydroboration reaction followed by a second step to remove the boron species to give the final alcohol product. The overall reaction is regioselective and is also stereoselective in both steps. Molecular rearrangements do not take place.

26. A) The addition of H^+ to the alkene (attack of H^+ by the alkene) results in one end of the alkene bearing a positive charge. This carbocation can rearrange under certain circumstances when a more stable carbocation can be formed from a rearrangement.
27. C) The alcohol shown in the scheme above comes from anti-Markovnikov addition of water across the double bond via the organoborane species followed by oxidation by peroxide as shown in equation I above. The other two equations describe Markovnikov addition of water to an alkene.
28. B) $NaBH_4$ in step II of equation 2 contains mostly H atoms not oxygen atoms. Its name is sodium borohydride and it is a supplier of hydride ion. Reduction is the addition of hydrogen to a molecule. H_2O_2 in step II of equation 3 is an oxidizing agent, it is hydrogen peroxide, it supplies oxygen. In this case the oxygen atoms bond to the molecule at the position where the boron atom was, therefore oxygen is thus added to the molecule i.e. an oxidation.

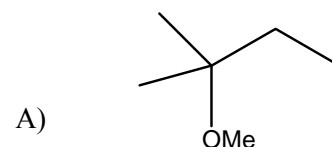
29. D) All alcohols show a broad band (OH stretch) in the IR spectrum from $3300-3500\text{ cm}^{-1}$

Passage VII (Questions 30 - 33)

A chemist was attempting to synthesize compound **B** from iodide **A** using MeOH as the nucleophile but the reaction was unsuccessful. Instead of obtaining the desired product **B**, an unknown molecule **C** was obtained. Molecule **C** gave 4 signals in the 1H NMR spectrum, one singlet integrating to 6H atoms, one singlet integrating to 3H atoms, a quartet integrating to 2H atoms and a triplet integrating to 3H atoms. **C** is the product of a reaction mechanism involving a molecular rearrangement step.



30.

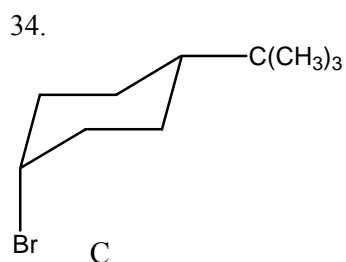


(A) is the only molecule which fits with the NMR data and also the fact that a molecular rearrangement has taken place. The molecular rearrangement takes place because **C** is formed by an S_N1 reaction rather than the S_N2 reaction desired by the chemist. The S_N1 reaction gives a primary carbocation intermediate which then rearranges to a more stable tertiary carbocation prior to attack by methoxide nucleophile giving compound **C**.

31. B) MeONa is the only MeO⁻ nucleophile in the list. This nucleophile is much stronger than MeOH and is more likely to give the desired S_N2 reaction to product B rather than the S_N1 reaction to product C.
32. A) Given the reaction conditions and that no promoting conditions for radical reactions are apparent answer (A) is the only sensible choice as carbocations are able to undergo rearrangements.
33. C) An S_N2 reaction inverts the stereochemistry at the carbon that the nucleophile attacks and an S_N1 reaction destroys the chirality at the carbon containing the leaving group leading to the planar carbocation intermediate.

Passage VIII (Questions 34 - 37)

The rate of the base-induced dehydrohalogenation reaction of *cis*-1-bromo-4-*tert*-butylcyclohexane is proportional to the concentration of both the bromide and the base, however that of the *trans* isomer is proportional only to the concentration of the bromide.



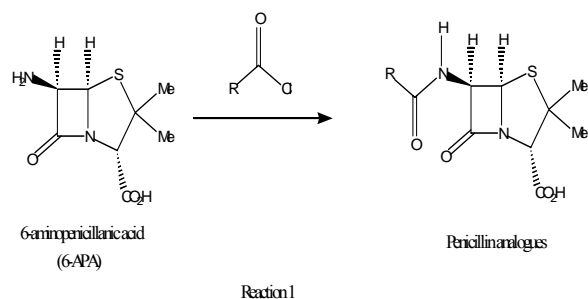
35. A) E2. Because the rate is proportional to both, the concentration of both the bromide and the base, and an elimination (dehydrohalogenation) takes place, reaction must proceed by an E2 mechanism.

36. (B)

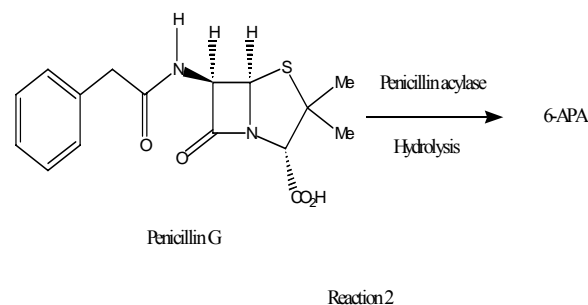
37. A) because rate is only proportional to the concentration of bromide, reaction must proceed by an E1 mechanism.

Passage IX (Questions 38 - 42)

Chemists investigating the antibiotic agent, penicillin G, wished to prepare a number of analogues which might solve the problem of bacterial resistance to this class of drugs. A method of production was required which was efficient and cheap. Chemists decided to start from 6-APA and following the scheme outlined in Reaction 1, they synthesized a number of analogues with a variety of groups at R.



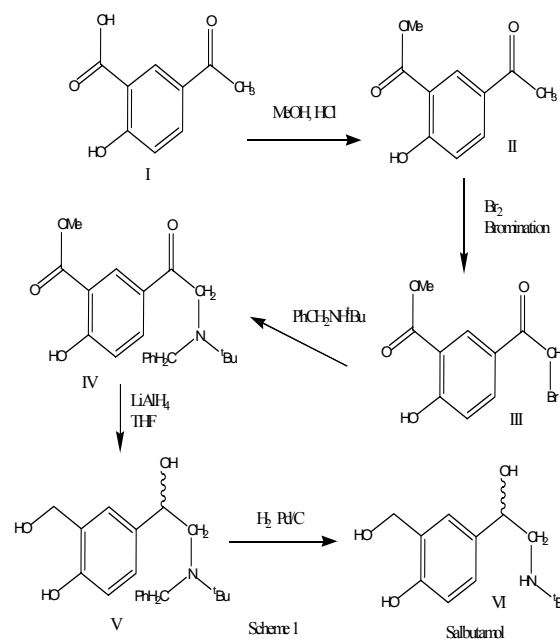
In order to obtain large enough amounts of 6-APA for this synthetic scheme, chemists used Penicillin G in an enzymatic cleavage reaction to form 6-APA (reaction 2).



38. C) II is the only reaction above which will give an acid chloride.
39. B) Friedel Crafts alkylation utilizes acid chlorides in reaction with an aromatic system and a Lewis acid catalyst to give an acylated aromatic product. Alcohols in reaction with an acid chloride give esters. Amines in reaction with an acid chloride give amides.
40. C) The result of hydrolysis of an amide is a carboxylic acid (C) and an amine (6-APA also has an amine group).
41. A) This is the only route that will form a dipeptide
42. D) 4
Say we used Gly and Ala. We would obtain Gly-Gly, Gly-Ala, Ala-Gly and Ala-Ala.

Passage X (Questions 43 - 47)

Salbutamol is an important molecule used for the treatment of asthma. It is a β_2 agonist and relaxes bronchial smooth muscle resulting in dilation of the airways. In the laboratory Salbutamol can be synthesized according to the reactions shown in Scheme 1.



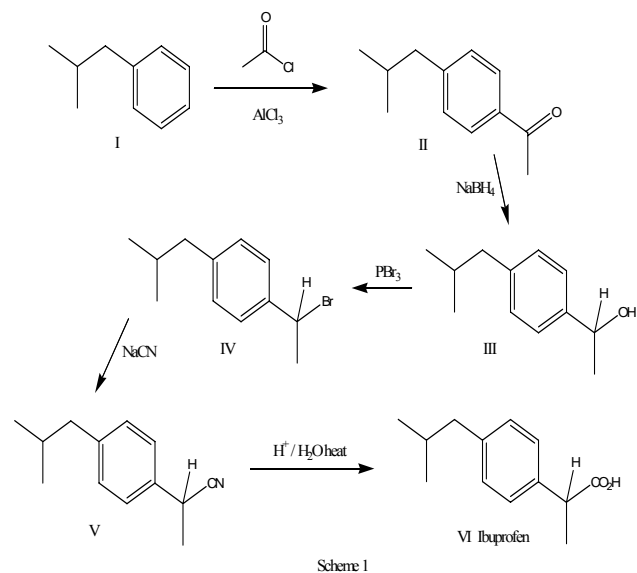
43. D) The reaction of an alcohol with a carboxylic acid under acidic conditions (HCl) is an acid catalyzed esterification.
44. D) The $\text{PhCH}_2\text{NH}^t\text{Bu}$ is a nucleophilic amine and it is reacting as a nucleophile with a primary halide. Primary halides most always react with nucleophiles in an $\text{S}_{\text{N}}2$ reaction.
45. B) LiAlH_4 is a reducing agent. Lithium aluminum hydride supplies H^- (hydride) ion which acts as a nucleophile at electrophilic centres. Overall the reaction is addition of H_2 to a molecule, which is a definition of reduction.

46. B) LiAlD_4 supplies D^- ion as a nucleophile which attacks electrophilic carbonyl centres. It is not responsible for the alcohol H atom which comes from either water or a protic solvent at the end of the reaction.

47. B) This is a catalytic hydrogenation and Pd/C is the catalyst

Passage XI (Questions 48 - 52)

Non steroidal anti-inflammatory agents (NSAIDs) are a successful class of compounds used for the treatment of pain and inflammation in a range of disorders and are especially useful in the treatment of arthritis. One such drug is Ibuprofen. In the laboratory chemists can prepare the racemic ibuprofen compound by many different routes. One such synthetic route is shown in Scheme 1 below.



48. B) The reaction is indeed a Friedel Crafts acylation and the AlCl_3 is a Lewis acid catalyst and so is usually present in less than equimolar amounts.

49. C) The reaction is a Friedel Crafts acylation which is an electrophilic aromatic substitution reaction. The alkyl group of molecule I is an ortho/para director.

50. B) The reaction is a reduction. NaBH_4 is sodium borohydride and H^- is the reducing species.

51. A) $\text{S}_{\text{N}}2$ reactions proceed with inversion of configuration at chiral centres (Walden inversion) and primary substrates are better than secondary or tertiary.

52. C) The conversion of a nitrile to a carboxylic acid is achieved by an acid catalyzed hydrolysis reaction.