1st Annual
Science Symposium
May 9, 1995
Paradise Valley Community College
Foreword

The 1st annual Science Symposium was held on May 9, 1995. Students enrolled in CHM 236 Organic Chemistry participated in the event.

Each contributor was responsible for selecting and researching their topic, preparing a paper and orally presenting their project to their peers. This booklet contains every one of those papers.

As faculty advisor and instructor for this course, I want to thank and congratulate each participant for their effort, courage and dedication. These individuals have established an event that will occur annually. I am both proud and honored to have worked with such a talented group of individuals.

William L. Mancini, PhD
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CONTRASTING TWO TOTAL SYNTHESSES OF TESTOSTERONE

BY DAVID MCKAY CHISHOLM

APRIL 25, 1995

CHM 236

The pathway from the tetracyclic ketone I to testosterone is detailed in two syntheses, both differing in practicality and efficiency. Synthesis 1 takes the ketone I and places a protective ketal group on the A carbonyl in order to protect the functionality of the a,b unsaturated ketone to the ketal II. Milds Nelson reduction afforded the anti-trans-dihydro ketal III, and upon further lithium reduction, the aromatic ring was taken down to provide two isomers with a,b unsaturation on the D ring, thus giving structures V and IV. Both of these isomers, upon catalytic hydrogenation (alkaline) were reduced to the ketone VI. Ring contraction began with treatment of VI with furfuraldehyde, which yielded a furfurylidene derivative VII, which easily methylated to two cis-epimers, the cis VIII epimer and the trans IX epimers (74% and 19% respectively). These isomers were successfully separated by chromatography, and then independently subjected to oxidation by use of alkaline hydrogen peroxide. Each reaction proceeded to give a crystalline dibasic acid, which by use of diazomethane, was converted to the dimethyl esters, VIII to X, and IX to XI. The ring closure via decomposition in inert p-cymene took the dimethyl esters X and XI to the cis and trans ketones XII and XIII, respectively. From here, Johnson et al. abandoned the ketone XIII until its use in a later experiment proved it incapable of being made into testosterone. However, their continued efforts in working with ketone XIII proved successful after its reduction to the dl-testosterone-3-ethylene ketal XIV, and then subsequent acid hydrolysis of the ketal group to dl-testosterone XV. Synthesis 2 proved to be the longer route, but more efficient. It started with ketone I, and reduced this to the alcohol II by three steps, all of which could be done concurrently in the same vessel. This alcohol was reduced by Birch reduction, followed by acid hydrolysis to the isomeric a,b unsaturated dehydro ketones III and IV. Hydrogenation of both these dehydro ketones over palladium-on-carbon afforded the same saturated ketone V in 80% yield. As in synthesis I, attention was now placed on the methylation ring contraction sequence. Again, condensation with furfuraldehyde gave the furfurylidene derivative VII (R = b-H, R' = H), and then replacement of R groups to the acetate VII (R = b-CH$_3$, R' = Ac). This now allowed the ring to be opened via bromination followed by treatment with hydrogen peroxide to yield the diacid VIII (R = H). The diacid was treated with diazomethane to the dimethyl ester VIII (R = CH$_3$) and then allowed to cyclize by means of a Dieckmann condensation with potassium t-butoxide in benzene, and hydrolysis and decarboxylation in the presence of acetic and hydrochloric acid to the 3-hydroxy ketone IX. The hydroxy ketone IX was oxidized by the Jones method to the 3,17 dione X. This dione was then oxidized to the 4,5 unsaturated dione XI, and then allowed to react with fermenting yeast to produce a mixture that included the desired product -- testosterone XII.

In this paper, two detailed syntheses of dl-testosterone are outlined with the acknowledgement that neither one of them is "better" than the other, but that both have their advantages and disadvantages. Both syntheses were obtained from W.S. Johnson et al., from the series STEROID TOTAL SYNTHESIS [1,2], and both start from the same tetracyclic ketone I, albeit proceed with distinct pathways.

The approach that is outlined first is the approach that offers a shorter pathway to the desired product (i.e., less steps), however it is the more restrictive route. Moreover, the second route will afford a higher yield.

The route first taken utilizes the protective capabilities of a cyclic ketal system[3] to avoid the
unnecessary reduction of the already existent, and desired 
$\alpha\beta$ unsaturated ketone ring. The reduction of this system 
would seem unpurposeful and perhaps costly since the end 
product maintains this functionality. However, as practical 
as this protecting group sounds, it too places some 
burdensome restrictions on the kinds of operations that can 
be performed in the synthesis [3]. The limitations are that 
acidic conditions must be avoided and any reaction that 
attacks olefinic bonds must be done with extreme 
selectivity. It will be shown that these limitations are 
obviated in the second synthetic route, which by the way 
does not include the production of a ketal group.

**synthesis 1**: The tetracyclic ketone I was given its 
protective ketal group by treating it with ethylene glycol 
to the ketal II. The styrene bond of this ketal (the 8,9 
double bond) was reduced via the WILDS NELSON conditions of 
lithium and alcohol in liquid ammonia. These conditions 
proved safe for the A/B unsaturation, giving a product of 
the anti-trans dihydro ketal III. This compound was given 
further treatment of the lithium reduction conditions and 
the aromatic ring was reduced. The loss of aromaticity was 
evidenced by UV spectra lacking any absorptions except end 
absorption (end absorption signaling an alkene or carbonyl, 
in this case the alkene in ring B). The incremental 
maintenance of the $\alpha\beta$ unsaturated ketone was verified at 
this stage via the opening of the ketal with the addition of 
dilute hydrochloric acid, thereby exhibiting UV absorption 
at maxima 240 nm..

The reduced products from II and III were treated with 
0.1 M aqueous methanolic oxalic acid, which was found not to 
be detrimental to the ketal group. This in turn produced an 
intermediate that had a carbonyl (IR peak at range of 5.85\mu) 
and $\beta\gamma$-unsaturation. Isomerization of this intermediate 
structure to the $\alpha\beta$ conjugation with the carbonyl was 
accomplished by adsorption on alkaline alumina (UV 
absorption at maxima 240-250 nm.) Purification of these 
products by chromatography gave two crystalline ketones, one 
melting at 176°C, (UV maxima 225 nm.) and the other melting 
at 143°C (UV maxima 246.5). These spectra told Johnson, et al., that they had structures V and IV, respectively.

While maintaining the ketal group in alkaline 
conditions, catalytic hydrogenation of V or IV yielded a 
product with the 5,6 double bond intact, that is, compound 
VI, m.p. 143°C. This structure was tested and verified by 
UV spectra with end absorption only (carbonyl and alkene of 
ring B). Johnson et al did not provide a percent yield but 
referenced to expectations of about 44% at this juncture.
The next step in procession was to convert the D ring to a 5-carbon ring system, thus making headway towards the desired 17-keto structure which is the immediate precursor to testosterone. This was accomplished by ring contraction via condensation. The reaction took place by use of furfuraldehyde. This proceeded to give a furfurylidene derivative VII, m.p. 188°C, which easily methylated to two cl3-epimers, VIII (cis) and IX (trans) in 74% and 19% yields, respectively. These isomers were separated by chromatography and then subjected to oxidation by alkaline hydrogen peroxide. This particular oxidizing agent was chosen due to its known selectivity and its ability to leave isolated olefinic bonds unaltered. Oxidation of the two isomers produced two crystalline dibasic acids, which were further changed to two isomeric dimethyl esters by use of diazomethane. The cis isomer VIII was taken to the dimethyl ester X (R= CH3), m.p. 123°C in 82% over-all yield. Similarly, the trans isomer IX was taken to the dimethyl ester XI (R= CH3), m.p. 163°C, in 92% yield.

Johnson et al attempted several methods for ring closure, including: 1. simple pyrolysis of the diacid, however this led to the problem of decomposition and the breaking up of the ketal group, 2. a Dieckmann condensation with potassium t-butoxide, this produced the β-keto ester XVI (R= CH3) with the desired 5-carbon ring, however subsequent saponification proved futile due to continued ring opening, and 3. decomposition while in an inert solvent. This last method proved fruitful in that the desired ketones XII (cis isomer) and XIII (trans isomer) were achieved after refluxing in p-cymene for one hour and two hours, respectively. The latter in 60% yield.

Johnson et al postponed any further utilization of the 13-iso ketone XII in this article, and then later in the second article [2], realized that they could not convert this compound into testosterone. It was not mentioned whether or not further investigation of this conversion would be completed.

In this synthesis, the 13-iso ketone XIII was taken further and comparisons were periodically made with the physical properties of its natural counterpart. For example, this ketone's m.p. 169°C. and its infrared spectrum were identical to that of authentic (naturally derived) d-XIII.

Reduction of the ketone XIII with sodium borohydride gave dl-testosterone-3-ethylene ketal (XIV), m.p. 181°C., which gave dl-testosterone (XV), m.p. 169°C., upon acid hydrolysis of the ketal. Again, Johnson et al report that
infrared spectra of these two substances were identical with those of the naturally derived substances. It was further reported that resolution of the stereoisomers was not conducted due to insufficient product, however it was said to be receiving further study.

**synthesis 2:** Four years later, Johnson et al published another synthetic route to testosterone. As mentioned earlier, this route has more steps than synthesis 1, but has the benefit of a higher yield and a less restrictive approach.

The same tetracyclic ketone I is used and instead of introducing a protective ketal group, the reduction of the $\alpha,\beta$ unsaturated ketone is allowed to occur. This is done stepwise by the following reactions. The 4,5 double bond is hydrogenated over palladium, reduction of the keto group to the alcohol is done by lithium aluminum hydride, and the 8,9 styrene bond is reduced by potassium and alcohol in ammonia, a milder version of the WILDS NELSON conditions used in synthesis 1. These successive steps render the alcohol II.

Via BIRCH reduction with lithium, ammonia and alcohol, the benzene ring was reduced to the hexadiene and then converted to the mixture of two isomeric $\alpha,\beta$ unsaturated ketones III and IV by acid hydrolysis (see mechanism "A").

These two isomers are the 13,14 (m.p. 137-138°C, maxima 248 nm.) and 16,17 (m.p. 130-132°C, maxima 225 nm.) dehydro ketones, respectively.

Hydrogenation of both dehydro ketones over palladium-on-carbon afforded the same saturated ketone V in 50% yield. This structure was confirmed by its conversion to a substance of known configuration, that of endocrine VI.

At this point, attention was placed on the methylation ring contraction sequence, just as was done in synthesis 1. Again, condensation with furfuraldehyde gave the furfurylidene derivative VII (R= $\beta$-H, R' = H). This compound was further altered by replacing the R groups to the acetate VII (R= $\beta$-CH$_3$, R' = Ac), which then was opened up by ozonization and subsequent treatment with hydrogen peroxide to yield the diacid VIII (R = H). This diacid was treated with diazomethane to the dimethyl ester VIII (R = CH$_3$) and then allowed to cyclize via Dieckmann condensation with potassium t-butoxide in benzene, and hydrolysis and decarboxylation in the presence of acetic and hydrochloric acid into the 3-hydroxy ketone IX. The infrared spectrum was found to be identical to that of naturally-derived IX.

The hydroxy ketone IX was oxidized by the JONES method (see "JONES OXIDATION") TO THE 3,17 DIONE X. By treating this dione with acetic acid and 1 mole equivalent of
bromine, followed by heating with lithium chloride in dimethylformamide, it was converted to the 4,5 unsaturated dione XI. Again, both compounds X and XI had their infrared spectra compared to that of their naturally derived counterparts with full congruence. The dione was allowed to react with fermenting yeast to yield a mixture, of which contained the desired product -- testosterone XII.

ACKNOWLEDGEMENT: I would like to take this time to thank my mentor, Dr. Hank Mancini, for his relentless devotion in teaching me (us) the pleasures of organic chemistry and for being there for support and guidance during those times that I lost perspective. Thank You very much!!
SYNTHESIS ONE:

JONES OXIDATION:

(NOTE: THIS METHOD RARELY ATTACKS DOUBLE BONDS PRESENT INSIDE A RING C3)
SYNTHESIS TWO:

\[ \text{BIRCH REDUCTION} \]

FOLLOWED BY ACID HYDROLYSIS

MORE STABLE
WORKS CITED


Organic Chemistry
Professor Dr. Mancini
Research Project

PHENOBARBITAL

Carla Ernst

Spring 1995
Abstract:

5-Ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione, or phenobarbital, is an anticonvulsant and is an important compound in the medical industry for use in treatment of epilepsy and asthma. Phenobarbital is a member of the barbituate family, and barbituates have been used as sleep inducers since 1903. Synthesis producing a high yield is very important in the production of phenobarbital, and it can be used with other compounds such as acetaminophen, ephedrine sulfate, glyceryl guaiacolate, and theophylline to create medicinal substances for specific purposes. Complications with Phenobarbital include degradation reactions such as hydrolysis, and human usage can lead to addictions that are fatal. (Remington 282, Soloman 917, ASU MARS).

Introduction:

Phenobarbital is referred to as 5-Ethyl-5-phenyl-2,4,6 (1H,3H,5H)-pyrimidinetrione, 5-ethyl-5-phenylbarbituric acid, phenylethmalonylurea, phenobarbitone, Luminol, Gardenal, Barbenyl, Barbiphenyl, Dormiral, Euneryl, Neurobarb, Barbipil, Lubrokal, Lubergal, Phenyrall, Crtectil, Nunol, Phenonyl, Phenobal, Noptil, Agrypinal, Eskabarb, Estilfen, Gardepanyl, and Somonal.

The molecular formula of Phenobarbital is C(12)H(12)N(2)O(3), the molecular weight is equal to 232.23g, and the melting point is between 174-178 degrees Celcius.

Phenobarbital is an anticonvulsant hypnotic sedative that can lead to addiction and in some cases death with overuse and abuse. If used properly however, Phenobarbital can be used for medicinal purposes in treatment of epilepsy and asthma.

Patents for Phenobarbital include Bayer (247,952 in 1911), Hoerlein (1,025,872 in 1912), and Kay-Fries Chemistry (2,358,072 in 1944). (Connors 1042).

The following page was obtained at the ASU library from the computer MARS program. It gives the name, structure, and a brief description of phenobarbital.
Barbituric acid can be used in the synthesis of Phenobarbital. Derivatives of barbituric acid are called Barbituates, and Phenobarbital is therefore a Barbituate. Barbituric acid is a pyrimidine that exists in several tautomeric forms including an aromatic ring. These are the tautomeric forms of Barbituric acid (Soloman 917):

\[\text{Diagram of tautomeric forms of barbituric acid} \]

Synthesis:

Synthesis and manufacture of Phenobarbital as a hypnotic and sedative in the treatment of epilepsy became very important in the U.S. during the War in 1918. Rising and Stirglitz investigated a four-step synthesis in the production of Phenobarbital. The synthesis is as follows:

1) Ethyl oxalate is condensed with the ethyl ester of phenylacetic acid by means of sodium ethylate in order to form the sodium salt of the diethyl ester of oxalyl-phenylacetic acid.

2) The dimethyl oxalylphenylacetate is ester is converted by heat into the methyl ester of phenyl malonic acid by the loss of carbon monoxide.

3) The ethylation of phenylmalonic methyl ester in alcoholic solution yields ethylphenylmalonic dimethylester

4) The condensation of ethylphenylmalonic dimethylester with urea yields phenyl barbituric acid.

This synthesis was found to produce a low yield, so further investigations regarding the Fischer method and the Grignard system were then investigated by Rising and Stirglitz. The Fischer method for preparing Phenobarbital is as follows:
Sodium methylate is prepared from 14.2g of absolute methyl alcohol and .9g of sodium. To it are added 2.5g of phenylethylmalonic methyl ester and 1.1g of urea. This mixture is heated in a sealed tube at 105-108 degrees Celsius for six hours. When the tube has cooled, the white precipitate is removed and the filtrate is again heated in a sealed tube for six hours at 105-108 degrees Celsius. Any further precipitate of sodium carbonate which has formed during the second heating is removed as before. The filtrate, which is alkaline, is neutralized with acetic acid, and the alcohol evaporated in vacuo. When the last of the alcohol is gone, the residue in the distilling flask has an oily appearance, and when a few cubic centimeters of water are added, a cloudy emulsion of the oil and water forms. This emulsion is now extracted with the ether, and the ether allowed to evaporate spontaneously. The residue is a mass of crystals in a thick oil, and is a mixture of phenylethylbarbituric acid and unchanged ester. It is extracted with ligroin of low boiling point, which dissolves the ester. The remaining white mass is purified by recrystallization from the boiling water, and after two recrystallizations, the product shows a melting point of 174 degrees Celsius. The crystals are pure white and lustrous. The yield is about 40 percent of the theoretical (Rising 723-25, 730).

The Australian Journal of Chemistry gives a synthesis for 5-Ethyl-5-phenylbarbituric Acid. The synthesis is as follows:

5-Ethylbarbituric acid (8b) (560 mg, 3.6 mmol) was added to a stirred solution of phenylethyl triacetate (1:83 g, 4.0 mmol) and pyridine (940 mg, 12 mmol) in chloroform (2ml) at 40 degrees Celsius and the volume was adjusted to 6 ml with chloroform. The mixture was stirred at 40 degrees Celsius for 4 h and then poured into ether (100 ml). The ether phase was washed with hydrochloric acid (1 M, 50 ml), dried (Na(2) SO(4)), filtered and the solvent removed. The residue was dissolved in acetone, filtered from residual salts and the solvent was removed to give 5-ethyl-5-phenylbarbituric acid (754 mg, 91%). This is identical with an authentic sample of phenobarbital (Aust. J. Chem. 1253).

On the following page is also a synthesis of Phenobarbital (Soloman 464).
These four outlined methods of synthesizing are unique manipulations of reagents to produce Phenobarbital in various quantities. Their variety exemplifies the diversity and creativity used in organic chemistry, and the increase in yield over the years proves that technology is indeed advancing. The reasons for performing these synthesis are that Phenobarbital was the first effective antiepileptic agent, it has relatively low toxicity, is inexpensive, and is one of the more effective and widely used drugs for this purpose. Anticonvulsant properties of Phenobarbital are the capacity to exert maximal anticonvulsant action at doses below those required for hypnosis (ASU Stacks 444).

Toxicity:

Complications involving Phenobarbital in the human aspect can be quite severe. Some of the adverse effects are sedation, nystagmus, ataxia, irritability and hyperactivity in children and agitation and confusion in the elderly, scarlatiniform, exfoliative dermatitis, hypoprothrominemia, and megaloblastic anemia (ASU Stacks 445). Because phenobarbital is a member of the Barbituate family, it also displays complications unique to the Barbituate family. These complications include addiction, a coma, overdose, poisoning, and sometimes even death. The potentially fatal dose of Phenobarbital is 6 to 10 grams (ASU Stacks 362).

Hydrolysis:

Hydrolysis is a degradation reaction that can occur within the Phenobarbital compound. One method of avoiding this degradation is to entrap the Phenobarbital molecules within the micelles. This will minimize the hydroxyl-ion attack responsible for the degradation. The greater the solubilizing effect of the surfactant, the greater the stabilizing effect. Polysorbate 80 and polyoxyethylene -20-cetyl ether form larger molecules because of their high molecular weights and lack of electrical charge, and have been found to have better stabilizing effects. Hydrolysis and degradation examples are shown on the following pages (Remington 285).
FIGURE 2. PHENOBARBITAL. Arrhenius plot for pheno- barbital hydrolysis at pH 6.8.

Stabilization Methods

The best way to inhibit the hydrolysis of pheno- barbital is to remove it from contact with water. Powders, tablets, and capsules are thus the preferred dosage forms.

A common method for minimizing phenobarbital degradation in solution dosage forms is to dissolve the drug in a mixed solvent of water and organic solvents such as alcohol, sorbitol, propylene glycol, glycerol, or polyethylene glycol (12, 13, 17-20). Among these, glycerin and ethanol have the greatest stabilizing effects. Ikeda (21) attributed the stabilization of barbiturates in alcohol-water mixtures to the inhibition effected by decreased dielectric constant on the reaction between ions of like charge. The activation energy of the solvolysis increased with decreasing dielectric constant.

Khalil, Moustafa, et al. (16) studied the kinetics of degradation of phenobarbital in model solubilized systems containing cetrimide, sodium lauryl sulfate, polysorbate 80, polyoxyethylene-20-cetyl ether, and a propylene glycol-water mixture, and reported the results shown in Table II.
TABLE II. Apparent First-order Rate Constants and Kinetic Parameters for the Degradation of Phenobarbital at pH 6.8 in Various Solubilized Systems

<table>
<thead>
<tr>
<th>Solubilizer</th>
<th>$k \times 10^7$ (s$^{-1}$)</th>
<th>$k \times 10^{10}$ (s$^{-1}$)$^a$</th>
<th>$t_{90}$ at 25$^\circ$ (yr)</th>
<th>Ea (kcal mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70$^\circ$</td>
<td>75$^\circ$</td>
<td>80$^\circ$</td>
<td>25$^\circ$</td>
</tr>
<tr>
<td>Standard solution</td>
<td>4.69</td>
<td>7.99</td>
<td>13.52</td>
<td>22.08</td>
</tr>
<tr>
<td>Sodium lauryl sulfate</td>
<td>2.63</td>
<td>5.38</td>
<td>9.99</td>
<td>4.01</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>1.77</td>
<td>3.20</td>
<td>7.11</td>
<td>1.08</td>
</tr>
<tr>
<td>Polyoxyethylene-20-cetyl ether</td>
<td>1.74</td>
<td>3.25</td>
<td>7.11</td>
<td>1.08</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>1.17</td>
<td>2.70</td>
<td>5.90</td>
<td>0.33</td>
</tr>
<tr>
<td>Cetrimide</td>
<td>7.87</td>
<td>13.52</td>
<td>17.12</td>
<td>137.63</td>
</tr>
</tbody>
</table>

$^a$By extrapolation.
Interactions:

Phenobarbital, primidone, phenytoin, and carbamazepine are potent inducers of the hepatic drug-metabolizing enzymes and have been shown to increase significantly the metabolic clearance of each other as well as of the other concurrently used antiepileptic drugs. Usually these interactions result in decreased serum levels and decreased clinical efficacy of "standard dose" of the affected drug. If the latter is converted to active metabolites, however, the situation may be more complex, and paradoxically, potentiation of therapeutic and/or toxic effects may occur (Richens 28). Table 2-1 on the following page displays the interactions of several compounds including Phenobarbital with active metabolites.

The metabolism of virtually all major anticonvulsants is vulnerable to inhibition by concurrently administered reagents. Many of these interactions are clinically important because the consequent increase in serum drug concentration can easily result in clinical signs of toxicity. An increase in serum phenobarbital levels, probably due to inhibition of metabolism may be caused by valproic acid, phenytoin, sulthiame, methsuximide, and pheneturide. Probably the most important among these interactions is that involving valproic acid. If valproate is given to patients stabilized on phenobarbital, serum phenobarbital levels will rise 25-50%. If barbiturate dosage is not reduced, sedation and other signs of toxicity may ensue (Richens 30-32). Table 2-2 on the following page lists the drug affected including Phenobarbitone along with several inhibiting drugs.

Conclusions:

Phenobarbital is a very powerful drug that can be used for medicinal purposes in the treatment of epilepsy and asthma. It is a drug of choice in the medical field because it is relatively non-toxic in comparison with other barbituates, it is effective, and costs less to synthesize. However, it should be handled and ingested with care so as to avoid any side effects or interactions that may occur.
Table 2-1. Some Antiepileptic Drugs Whose Metabolism May Be Stimulated by Enzyme Induction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Active metabolite</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clobazam</td>
<td>N-desmethyliclobazam</td>
<td>9</td>
</tr>
<tr>
<td>Clonazepam</td>
<td></td>
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</tr>
<tr>
<td>Diazepam</td>
<td>N-desmethyldiazepam</td>
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</tr>
<tr>
<td>Carbamazepine</td>
<td>10,11-epoxide</td>
<td>12</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Primidone</td>
<td>Phenobarbital, PEMA</td>
<td>16</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td>17</td>
</tr>
</tbody>
</table>

Table 2-2. Inhibition of the Metabolism of Phenytoin, Phenobarbitone, and Carbamazepine by Other Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Drug affected</th>
<th>Inhibiting drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Sulthiame</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Phenobarbitone</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Methsuximide</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Denzimol</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Nafimidone</td>
<td>28</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>Valproate</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Sulthiame</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Methsuximide</td>
<td>26</td>
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<tr>
<td></td>
<td>Pheneturide</td>
<td>32</td>
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<tr>
<td>Carbamazepine</td>
<td>Valpromide</td>
<td>33–36</td>
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<tr>
<td></td>
<td>Valproate</td>
<td>37</td>
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<td></td>
<td>Diltiazem</td>
<td>39</td>
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<tr>
<td></td>
<td>Verapamil</td>
<td>38</td>
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<tr>
<td></td>
<td>Denzimol</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Nafimidone</td>
<td>28</td>
</tr>
</tbody>
</table>
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ASU MARS

ASU Stacks


Hypnotics and Sedatives; Ethanol. Ch 17. 360, 362.
Bradley J. Fisher
Organic Chemistry 236

Abstract

Naproxen or 2-(6-methoxy-2-naphthyl) propionic acid was conveniently prepared by reacting 2-chloro-2-alkylthio-propionate and 2-methoxynaphthalene in good yield. A method using a Friedal-Crafts reaction followed by desulfurization by the use of Raney Nickel and finally subjected hydrolysis. This method was also found to be applicable to other electron-rich aromatic compounds.

Naproxen, Equiproxen, Naprosyn, or 2-(6-methoxy-2-naphthyl) propionic acid, the topic of my research had been one of the most widely used and prescribed anti-inflammatory pharmaceuticals in the United States for several years. This drug, which has several names besides it's IUPAC nomenclature listed above in this paragraph, has been synthesized in good yield (in most cases 95% or better) and has shown to have 2 favorable biochemical advantages on living organisms being an anti-inflammatory and an analgesic.

There has been several different approaches to synthesizing this pharmaceutical but the most comprehendable has been the Friedal-Crafts approach because of it's favorable yield and easy application of this electron-rich aromatic structure which I will hence forth refer to as

\[ \text{Naproxen.} \]
The synthesis of Naproxen is one of several steps using a Friedal-Crafts method and it is described below:

In 8.0 g of carbon tetrachloride, 1.48 g (1.05 eq moles) of ethyl 2-methyl-thiopropionate was dissolved, and 1.48 g (1.16 eq moles) of N-chlorosuccinimide was added thereto at 20°C. This solution was then stirred for an hour and a half at 20°C. This reaction mixture was promptly filtered and washed with 6.0 g of carbon-tetrachloride, whereby the succinimide floating in the form of crystals was filtered off. The carbon-tetrachloride solution of ethyl 2-chloro-2-methyl-thio-propionate was thus obtained. The structure is shown below.

\[
\begin{align*}
\text{CH}_3 & \\
\text{Cl} & \\
\text{C}_2\text{H}_5 & \\
\text{SC}_2\text{H}_5 & \\
\end{align*}
\]

This was in turn added dropwise from 25°C to 30°C to a solution of 2-methoxynapthalene. That structure is shown below.

After the completion of the addition, stirring was continued for 45 minutes at the same temperature. These results were then poured into icewater, and the organic layer was washed with water and thereby concentrated by reduced pressure, the product was an oily substance weighing 2.75 g of ethyl-2-methylthio-2-(6-methoxy-2-napthyl) propionate. The structure is shown on the next page.
Then, in search of a higher yield, the ethyl-2-methylthio-2-(6-methoxy-2-napthyl) propionate was desulfurized by Raney Nickel giving ethyl-2-(6-methoxy-2-napthyl) propionate in more than a 95% yield. The reaction is shown below.

Then the product was put under hydrolysis to give Naproxen in a better yield of over 95%. The reaction is shown below.

In past routines the methods to obtain Naproxen were long and tedius with several steps involved. This method has conquered both of these obstacles. The only known drawback of this synthesis is the need to make the starting materials that are with little impurities. This will in turn cause a lower yield and also a less pure one. Once a crude product was found, it has been determined that the ease of
adding Raney Nickel followed by hydrolysis is worth the 95% yield final outcome.
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Synthesis of Capsaicin

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Chemistry 236
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Synthesis of Capsaicin

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*Five of the piquant ingredients found in chilli peppers, the Capsaisinoids, have been efficiently synthesized by Kaga et. al. The synthetic process of capsaicin, one of the most abounding and most pungent, is shown here excerpted from their report in Japan Society for Bioscience, Biotechnology, and Agrochemistry. This method involves a Wittig reaction between isobutytri phenylphosphorane and an appropriate lactol, followed by the nitrous acid-induced isomerization of the subsequent (Z) and (E)-olefins.*

The chemical in hot peppers that causes this burning is capsaicin... the most fiery of a half dozen alkaloids found in the soft, seed-bearing core of the hot varieties (not in the seeds themselves, as most timid chili-eaters are often warned) "(McCort 48). Ironically the same compound that causes this burning is also a powerful pain killer or analgesic (Gurfeld 50). Capsaicin, as an herbal extract, has long enjoyed a popularity not only in native American tradition but also among European homeopathic practitioners, who at one point claimed it to be a cure-all. Recently some of these claims have in fact been substantiated by medical science, taking capsaicin from a little known naturopathic cure-all to a familiar drug store medication.

Two of the capsaicinoids "capsaicin and dihydrocapsaicin together make up 80 - 90 % of the capsaicinoids found in the fruit. In C. annum the total capsaicinoid content ranges from 0.1 to 1.0 %, and the capsaicin: dihydrocapsaicin ratio is about 1:1" (Govindarajan 435). There are also three other major capsaicinoids, nordihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin. They can be extracted from the peppers in many ways but are "practically insoluble in cold water; freely soluble in alcohol, ether, benzene, chloroform; slightly soluble in CS2." (Windholz 244).

The synthesis of capsaicin is important because of its relative inabundance in nature and its powerful help to those suffering from pain associated with AIDS, Cancer, Arthritis, neuralgias, shingles and diabetes. And its useful care can lead to total relief from pain in a short period of time and give independence from potential harmful side effects of other drugs.

As part of their studies on the biologically active components of spices, Kaga and his colleagues related an easy procedure for the synthesis of capsaicin. The Wittig reaction using isobutyraldehyde, followed by the nitrous acid-induced isomerization of the resulting (Z)-major olefin, had served as the route to capsaicin. To test the versatility of the key-step reactions, they tried to use lactols as the aldehyde sources for the Wittig reaction, in which the polarity of the Wittig reagent-aldehyde combination is inverted to that in the reported route. The experimental results of these studies are shown and annotated below.
Experimental

(Z)-1-Hydroxy-9-methyldecal-7-ene (4d): Characteristic procedure for the (Z)-olefins
(4). (372mg, 2.91 mmol) 7-Heptanolide (28) was dissolved in 11 ml of dehydrated toluene,
then cooled to -78 C. 3.2ml (3.2 mmol) of 1.0M DIBAL in toluene solution was added
dropwise to the solution. The reaction mixture was stirred for 1 hr. and extinguished by
addition of saturated HN3Cl, approximately 0.2ml . The combination was filtered through
Na2SO4 on a Celite pad and (2.5ml) dry DMF was added to the filtrate. This mixture was
evaporated using a vacuum pump for 10 minutes to eliminate the presence of toluene and
moisture. The unrefined lactol (2d) was added over a course of 10 min. to a solution of
(1.418g, 3.49 mmol) isobutyltriethylphosphonium bromide and (434 mg, 3.78 mmol)
KOBu ' in (12 ml) dry DMF under an atmosphere of argon at 0 C for 15 minutes. The
mixture was then stirred overnight at room temperature, diluted with (20ml) hexane, and
quenched with (10 ml each) saturated brine and water. The hexane layer was separated and
the aqueous layer was distilled with 2 -10 ml portions of hexane . The combined
distillates were washed with (10 ml) of brine and desiccated over anhydrous Na2SO4.
Evaporation of the solvent and purification of the remainder by column chromatography
on silica gel.

(E)-1-Hydroxy-9-methyldecal-7-ene (5d); typical procedure for the (E)-olefins (5).
(238mg, 1.29 mmol) of 4d was heated to 75 C under an atmosphere of argon. To this a
solution of (55ul) of 2M NaN2O3 and (25ul) of 6N HNO3 was added. The mixture was
stirred vigorously for 1 hour, neutralized with saturated NaHCO3 solution, and diluted with
ether. The organic layer was washed with saturated brine, dried over (Na2SO4). and
refined by silica gel column chromatography (10g. AcOEt: hexane=1.3) to give a 90%
yield of 5d (276mg) as a pale yellow oil, which was discovered to be a (E)-major olefin in
a 10:90 Z/E proportion by GLC analysis (column temperature. 120 C: retention time. 12.9
min./13.4 min.).
(E)-9-Methyldeca-7-enoic acid (6d); Typical procedure for the carboxylic Acids (6).
(252mg, 1.48 mmol) of the alcohol 5d was dissolved in (7.5ml) acetone, cooled to 0 C.
and treated with (1.5ml) of the standard Jones reagent 29). Following treatment at 0 C for
30 min., and then heating at room temperature for 1.5 hr. The surplus Jones reagent was
destroyed by addition of (1.0ml) 2-propanol. The mixture was filtered through a Celite
pad, which was washed with ether. The filtrates were concentrated under reduced
pressure. The residue was saturated with (NH4)2SO4, extracted with 4-3 ml portions of
ether, washed with saturated brine, dried with MgSO4, and purified by silica gel column
chromatography (10g, hexane: AcOEt=10:1-1:1) to yield a pale yellow oil.

(E)-N-(4-Hydroxy-3-methoxybenzyl)-9-methylene-7-enamide (Homocapsaicin 1d);
Typical procedure for the capsaicinoids. A stirred solution of (426mg, 2.26 mmol) of the
acid 6d and (0.49ml, 6.78 mmol) SOCl2 was refluxed for 2 hr., and the surplus reagent
was separated in vacuo. The resulting acid chloride was dissolved in (8ml) of dry ether,
and added to a stirred suspension of (726 mg, 4.75 mmol) vanillylamine in (12ml) ether.
The mixture was allowed to be stirred at room temperature for 2 hr. and then refluxed for
2 hr. Precipitated salt was separated by suction filtration, and the filtrate was condensed.
The residue was purified by silica gel column chromatography (25 g, AcOEt: hexane+1:2)
to give a colorless solid (656 mg, 91%).

**Structure Determination**

Confirmation of the structure of the products was done for each step using both IR
and NMR. The first product (4c) gave a 58% yield with a 93:7 (Z/E) ratio, and was run
neat on the IR showing charachteristic peaks at 3327 cm⁻¹ for -OH and 743 cm⁻¹ for the
-C=C group. NMR found δ values at 0.94 (-CH3 x 2), 1.24 (-OH), 1.35-1.40 (C4-H), 1.50-
1.62 (C2-H), 2.00-2.09 (C5-H), 2.52-2.65 (C8-H), 3.65 (C-H), and 5.14-5.25 for CH=CH.

The second product (5c) gave a 88% yield with a 11:89 (Z/E) ratio, and was run neat
on the IR showing charachteristic peaks at 3336 cm⁻¹ for -OH, and 968 cm⁻¹ for the C=C
group. NMR found δ values at 0.96 (-CH3 x 2), 1.27 (-OH), 1.32-1.43 (C2-H), 1.57 (C2-
H1), 1.94-2.02 (C8-H), 2.14-2.28 (C8-H), 3.64 (C-H), and 5.33-5.37 for CH=CH.

The third product (6c) gave a 78% yield, and was run neat on the IR showing
charachteristic peaks at 3300-2500 cm⁻¹ for -COOH, 1711 cm⁻¹ for -C=O, and 970 cm⁻¹
for the -C=C group. NMR found δ values at 0.96 (-CH3 x 2), a quintuplet at 1.40 (C4-H),
a quintuplet at 1.64 (C2-H), 2.00 (C5-H), 2.17-2.29 (C8-H), 2.36 (C2-H), and 5.31-5.38
for the -C=C group.

**(E)-N-(4-Hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide**

![Chemical Structure](image)

(Capsaicin 1c) gave a yield of 89% as a crude crystalline solid and when refined
was 65%. It was shown to have a melting point of 64-65 C. 30). Anal. Found: C, 70.62; H,
9.01; N, 4.51. Calcd. for C18H27NO3: C, 70.79; H, 8.9; N, 4.59%. This reveals that the
physical characteristics of the compound made are nearly identical to those for capsaicin extracted from members of the *Capsicum* species.
References


NICOTINE

Greg Myers
CHEM 236LL
April 26, 1995
Nicotine is a liquid alkaloid which can be extracted from dried leaves of tobacco. Nicotine is also known chemically as (S)-3-(1-methyl-2-pyrroldinyl)pyridine. This alkaloid is a colorless to amber colored oil that has a strong tobacco odor with an intensely bitter, burning taste. Nicotine's boiling point is between 123-125 degrees Celsius at a pressure between 15-20 mmHg. The density of nicotine is known to be 1.0097 at 20 degrees Celsius. Nicotine is soluble in water. It has no problem forming salts with mineral acids, for example hydrogen chloride, hydrogen bromide, and sulfate. The sulfate has been used in agricultural insecticides since it is easily soluble in water or alcohol. Nicotine is also extremely toxic. "Symptoms include extreme nausea, vomiting, evacuation of intestines and urinary bladder, mental confusion, and convulsions" (Wagner 663). Nicotine is believed to be lethal at an oral dosage of 50-60 mg/kg. Derivatives of nicotine are also used in the synthesis of vitamin B. Nicotine, like all other alkaloids, can be found in plant life; however, it can now be synthesized in a laboratory setting.

The Synthesis of Nicotine from Pyridine

\[
\begin{align*}
\text{Pyridine} & \xrightarrow{\text{H}_2\text{SO}_4, \text{SO}_3^+} \text{Pyridine-SO}_3^+ \\
\text{Pyridine-SO}_3^+ & \xrightarrow{\text{NaCN}} \text{Nicotine} \\
\text{Pyridine-CN} & \xrightarrow{\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{CH}_2\text{MgBr}} \text{Nicotine-C(OH)}_2 \\
\text{Nicotine-C(OH)}_2 & \xrightarrow{\text{HONH}_2, \text{LAH}} \text{Nicotine-NH}_2
\end{align*}
\]
In step one Pyridine is converted into Pyridinsulfonic acid. This is achieved by reacting Pyridine with Sulfur trioxide and concentrated Sulfuric acid. This reaction is an electrophilic aromatic substitution. Pyridine will break one of its double bonds to bond with Sulfur trioxide. In addition, sulfur also breaks a double bond with one of its oxygens forming cation. Sulfuric acid then loses one of its hydrogens to the cyclic ring, stabilizing the Arenium ion. Finally, the ion is protonated using acidic water and forms Pyridinsulfonic acid.

In step two Pyridinsulfonic acid is reacted with NaCN to form 3-

Pyridinecarbonitrile. This reaction is a nucleophilic aromatic substitution. The occurrence
of this reaction is due to the fact that the sulfur group is a good leaving group in addition to the CN group being an extremely good nucleophile.

In step three 3-Pyridinecarbonitrile undergoes a Grignard synthesis to produce β-Pyridyl-γ-ethoxypropyl Ketone. The polarity of the Grignard reagent propagates the attack of the nitrile group, forming a magnesium salt of an imine. The protonation of this salt results in the formation of the imine. The imine can then be protonated with acidic water to form β-Pyridyl-γ-ethoxypropyl Ketone.

In step four of the synthesis of Nicotine from Pyridine, β-Pyridyl-γ-ethoxypropyl Ketone is reacted with Hydroxylamine to produce an imine, or Schiff base. The polarity of the Hydroxylamine attacks the carbonyl group resulting in the breaking of the carbonile and adding Hydroxylamine to the carbon. This addition forms a cation at the nitrogen
center and an anion on the previously double-bonded oxygen. Reacting this product with acidic water allows the anion on the oxygen to attract a proton from solution to form an OH group. Also reacting this product with water allows the cation of the nitrogen to lose one of its hydrogens due to the polarity of the water, forming Carbinolamine. By further protonating Carbinolamine, a cation is formed on the OH group. This step is then followed by the loss of water, forming a cation at the nitrogen as a result of carbon double bonding with nitrogen. This ion is then reacted with water, which removes a hydrogen from the ionically charged nitrogen to form an imine or Schiff base.

In step five the Schiff base from step four undergoes a LAH (lithium ammonium hydroxide) reaction to form 1-[β-Pyrindyl]-1-amino-4-ethoxybutane. This reaction is a reductive amination which results in the reducing of the imine by adding hydrogens.
In step six 1-[β-Pyrtdyl]-1-amino-4-ethoxybutane reacts with Hydrobromic acid to form 3-[β-Pyrtdyl]-3-aminopropanol. In this step the Hydrobromide does two things. First, the hydrogen creates a cadion at the oxygen due to the addition of hydrogen. Second, the remaining bromide, being a strong nucleophile, cleaves the ethyl group from the end of the chain, forming 3-[β-Pyrtdyl]-3-aminobutanol.

In step seven 3-[β-Pyrtdyl]-3-aminopropanol reacts with methyl Iodine and methanol to form nicotine. The polarity of the amino group from 3-[β-Pyrtdyl]-3-aminopropanol reacts with methyl Iodine to form a cation on the nitrogen for the purpose of adding the methyl group to the nitrogen. The Iodine ion in solution then removes a hydrogen from the nitrogen, eliminating the cation. Then 3-[β-Pyrtdyl]-3-N-methylanminopropanol is protonated to form a cation on the hydroxy group. This cadion then reacts with the polarity of the amino group to form a secondary ring as well as a
cation at the nitrogen. Again, an iodine ion is used to remove a hydrogen from a nitrogen, forming Nicotine.


Niacin
(Nicotinic Acid)

Ona Papageorgiou
Organic Chemistry
Spring 1995
Abstract

Niacin (or nicotinic acid) is a vitamin that all humans need. The lack of it could eventually lead to death. Although it is found in nature it is a relatively simple compound and therefore there are many ways to synthesize it. Beginning with pyridine I will discuss the three most efficient ways to synthesize niacin. The first is a simple electrophillic aromatic substitution with a Lewis acid followed by oxidation. If we halogenate pyrine first one may also perform a Grignard to synthesize. Finally we can again begin with a simple halogenation, then react with a cyano group. This would actually be a nucleophillic aromatic substitution.

Niacin is the common name for Nicotinic acid. Niacin is a white crystalline acid that is a component of the vitamin B complex. It is found in fruit, meat, wheat germ, dairy products, and yeast. It is a biologically important amine and without it humans develop a deficiency disease called Pellagra which eventually leads to mental disorders. As we can see Niacin is very important to our well being.

There are various ways to synthesize Niacin from pyridine. The most simple being an alkylation followed by oxidation. We can also perform a halogenation followed by a Grignard. In addition we can perform halogenation followed by a cyano reaction followed by hydrolysis. These three methods are the most straight forward and most efficient, therefore, even though there are many other methods of preparation, I will only discuss these three.
The first method mentioned above is an electrophillic aromatic substitution. We begin with pyridine and perform a simply alkylation with CH$_2$Cl and the Lewis acid AlCl$_3$.

![Chemical Reaction Diagram]

The product is substituted at the three position by the methyl group. The reason that it is substituted at the three position rather than the one or four position is because there is more resonance. The molecule is going to be "happier" with more resonance. The resonance structures are as follows:

\[
\text{CHCl} + \text{AlCl} \xrightarrow{\text{CH}_3^+ + \text{AlCl}_4^-} \]

At other positions we do not have as many resonance structures. Our next step would be to oxidize the product from above. A common oxidizing agent is Potassium Permanganate so that is what I will use. We will react that with H$^+$ to produce our final product of Niacin.

![Chemical Reaction Diagram]

This method involves the least amount of steps and is the easiest way to synthesize Niacin, therefore it is preferred.
Another way to synthesize Niacin is utilizing the Grignard synthesis. In this reaction we cannot have any hydrous material involved because it will reverse the Grignard. We begin with standard pyridine and perform a halogenation. We react it with bromine and ferrous bromide.

\[
\begin{array}{c}
\text{Br}_2 \\
\text{FeBr}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{Br}^ullet
\end{array}
\]

Our product will be 3-Bromo-pyridine. The bromine is substituted at the three position as explained above because of resonance. We now are able to perform the Grignard, we will react the 3-bromo-pyridine with magnesium and ether.

\[
\begin{array}{c}
\text{Mg} \\
\text{Ether}
\end{array}
\rightarrow
\begin{array}{c}
\text{Mg}^ullet \\
\text{Br}^ullet
\end{array}
\]

Our product is our Grignard reagent. MgBr substituted at the three position on pyridine. Finally, we can react the product with carbon dioxide and H+. This will knock off the MgBr, which is now a good leaving group, and replace it with the carbon dioxide and the H+ will add on to the oxygen without the double bond.

\[
\begin{array}{c}
\text{Mg}^ullet \\
\text{Br}^ullet
\end{array}
\rightarrow
\begin{array}{c}
\text{C-O}^ullet
\end{array}
\rightarrow
\begin{array}{c}
\text{C-OH}
\end{array}
\]

We use this Grignard method when there is no water involved with any part of the reaction. Water would make the synthesis not work.
The final way to synthesize Niacin that I will discuss is using a cyano group. The only reason that I am able to use this method is because the cyano group is very reactive and it has to be in both acid and base. The first step will be to halogenate the same as I did in method #2:

\[
\begin{align*}
\text{N} & \quad \xrightarrow[\text{FeBr}_3]{\text{Br}_2} \\
\end{align*}
\]

Now that I have a good leaving group (bromine) I will react it with CuCN. Since there is a triple bond between the carbon and the nitrogen it becomes very reactive. This is in fact a nucleophilic aromatic substitution. The next step is produced with heat. We need to heat during the reaction and distill the product.

\[
\begin{align*}
\text{N} & \quad \xrightarrow[\text{Heat}]{\text{CuCN}} \\
\end{align*}
\]

The product is 3-cyanopyridine. This step is seen in the lab as a black viscous reaction and the black material is then distilled and solidified. It is then recrystallized with ligroin and easily converted into Niacin by hydrolysis:

\[
\begin{align*}
\text{N} & \quad \xrightarrow[\text{H}^+]{\text{H}_2\text{O}/\text{OH}^-} \\
\end{align*}
\]
This method requires much more lab time and effort. In addition it creates a lower yield than the first method. But when you want to have both acid and base this can be the preferred method.

These three methods must be used in different conditions depending on the lab, time and preference, that is why all three were discussed. We are able to perform simple alkylation followed by oxidation if time is a concern. We can perform a Grignard if no water is involved, or we can react with a cyano group if we want to work with both acid and base.
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MERC index. 1990.
ABSTRACT:

Benzo[a]pyrene is a member of the polycyclic aromatic hydrocarbon family and, unlike most other polycyclic structures, it has been proven to be extremely carcinogenic in mice and human tissue. It is released into the environment as a harmful by-product when burning organic matter from sources such as heat and power generation, refuse burning, and coke production. BaP’s physical properties are: MW=252.3 g, composition=95.21% carbon and 4.79% hydrogen, MP=178°C, BP=475°C, and soluble in hydrocarbon solvents. It is a florescent molecule which resides as a yellow solid occurring in two crystal forms, monoclinic and orthohombic.
INTRODUCTION:

Benzo[a]pyrene (BaP) belongs to the large class of polycyclic aromatic hydrocarbons which are found in the atmosphere, soil, and waterways. BaP is an inert molecule which can easily be metabolized into a highly carcinogenic epoxide derivative and should not be confused with its noncarcinogenic isomer Benzo[e]pyrene. The latter molecule, BeP, has attracted little attention because of its benign properties but is often used as a negative control in BaP studies. This paper shall focus on the nomenclature of BaP, different methods of BaP synthesis, the mechanisms of BaP synthesis from pyrene, and how BaP is metabolized by tissues to produce carcinogens.

NOMENCLATURE:

Benzo[a]pyrene's name follows the guidelines of the International Union of Pure and Applied Chemistry and the carbons are numbered as shown above. The bonds indicated double in the diagram have more double-bond character than those marked as single. The term 'K-region' is a name for the highly reactive bonds of the molecule that has been used for the 4,5 bond. A chemist named Pullman theorized poly-hydro-
carbons with K–regions are easily metabolized into carcinogens and poly–hydrocarbons with L–regions are carcinogen deactivators. This theory has been disproved by another chemist P. Sims whose studies have shown the Bay–region, carbon 10, 10a, 10b, and 11 are the reactive sites for carcinogenisis. This area is oxygenated into an epoxide and is highly reactive toward DNA. This mechanism is also dependent on the 7.8.9.10–ring which is referred to as the 'benzo–ring'.

BaP's UV spectra verifies the poly–aromatic ring characteristics by showing maximums at 214, 225, 254, 265, 284, and 296. A fused six membered ring has the base number of 214 nm and a conjugated diene with double bonds in the same ring have a base number of 253 nm, thus these maximums are theoretically expected. NMR spectra show readings between 6.8 and 8.2 ppm which verifies benzene activity. Fluorescence spectra illustrates the molecules flourescent activity with emission peaks at 406, 430, and 457. The emission peaks illustrate electron transition from the first excited singlet state to various vibrational levels of the ground state. See spectroscopy graphs at the back of this paper.

SYNTHESIS:

Benzo[a]pyrene can be synthesized from smaller ring systems and these syntheses are classified by the precursor to BaP. They are:
The Benzanthracene approach isn’t a very good option because it’s limited by the difficulty of making the starting materials. The Benzanthrene synthesis is a prime choice if you want to produce 1-, 2-, 3-, 11-, and 12-derivatives with either Me or OH substituents. 4- and 5-substituted BaP are produced from the Chrysenes technique. Perinaphthene is especially good for the synthesis of 6-substituted BaP and it’s starting materials are cheaply produced from 2-naphthol and glycerol. The final preparation of BaP from Pyrene was the original technique by J. Cook in 1933 which later chemists found messy and unpredictable. Through trial and error these steps have been improved and we shall discuss them here further in detail.
A. succinic anhydride condensation with aluminum chloride (Friedel–Crafts) in nitrobenzene gives beta-1-pyrenoylproponic acid

B. reduction by boiling with zinc dust or Wolf–Kishner reduction gives sodium salt of 1-pyrenoylproponic acid

C. HF catalyzed ring closure with zinc or stannic chloride gives gamma-1-pyrenylbutyric acid

D. selenium at 330°C or distillation from zinc gives 7,8,9,10-tetrahydronidozeno[a]pyre-7-one in low yields

E. zinc hydrazine gives 1-keto-2-ethyl-1,2,3,4-tetrahydronaphthalene

F. dehydrogenation by heating selenium at 330°C gives better yield of benzo[a]pyrene

The first step is a benzene ring addition through succinic anhydride condensation using the Lewis base aluminum chloride in nitrobenzene. This step is highly reactive due to the nitro group and produces a 90% yield. It is a Friedel–Crafts reaction which the position of substitution depends upon the nature of the acid chloride or anhydride.
This second step is the most capricious stage which tends to produce much pyrenyl-
butyrolactone byproduct but is diminished if reduction occurs at 200°C. We are familiar with the Wolf–Kishner reduction method with hydrazine/alkali/glycol. Hydrazone is first formed then the strong base brings about an isomerization of the hydrazone to a C–N=NH structure. Base catalyzed elimination of a basically stable nitrogen molecule creates enough energy for the reaction.

Step three can be catalyzed by zinc or stannic chloride, yet better yields are recovered when converted to the acyl chloride with thionyl chloride/pyridine and cyclization with stannic chloride. This product 7,8,9,10-tetrahydrobenzo[a]pyrene–7-one is commercially available.

The fourth step is a precursor to BaP but only produces a moderate yield. BaP production can be accomplished by condensation with selenium at 330°C or distillation from zinc dust. The former reaction is essentially dehydration and the selenium plays the part of an intramolecular hydrogen carrier.

Step five repeats the second step reducing the molecule with zinc, hydrazine, and copper chromite. The final step, which produces BaP in good yield, by dehydrogenation of BaP’s precursor when heated to 330°C with selenium is a repeat of the fourth step.

The pure form of BaP was not found to be carcinogenic but a metabolite BaPDE that is produced by oxidation of BaP–7,8-dihydriodiol is highly carcinogenic. This explains why BaP creates tumors in mice faster when injected into the bloodstream directly where there is found a high source of oxygen. The BaPDE covalently bonds to DNA by alkylations and the cells thus give rise to tumors. There are many inhibitors
of carcinogenesis (i.e. phenols, hexadecane, etc) and their mechanisms remain in doubt. Do note these inhibitors prevent the binding of BaPDE to DNA, not the metabolism of BaP to BaPDE.

7,8-DIOL-9,10-EPOXIDE
Ultraviolet absorption spectrum of BaP.

NMR of BaP.

Fluorescence Spectra of BaP.
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FULLERENES

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CHM. 236
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ABSTRACT
The Buckminster Fullerene is a spherical molecule of pure carbon having 60 or more atoms. The molecules are formed by the condensation of carbon soot at very high temperatures, in a helium atmosphere. The material exhibits a resonance throughout the entire molecule, and is extraordinarily stable. It does not degrade upon exposure to air or light. Uses are planned in the medical, chemical, and electronics industry and await the scientist or engineer that can develop methods of synthesizing and collection of mass quantities of this new product.

INTRODUCTION

The 18th century mathematician, Leonard Euler, calculated that an object consisting of hexagons and pentagons must contain a minimum of 12 pentagons in order to close into a sphere. In 1985, Professors, Robert F. Curl, Richard E. Smalley, of Rice University, and Professor Harold Kroto of the University of Sussex, theorized a pure carbon molecule having the shape of a soccer ball, and devised a device mechanism and collection system with which they synthesized the first known sample, and named the molecule after the American engineer, R. Buckminster Fuller, who designed and invented the well-known geodesic dome (4).

Known as Buckminsterfullerene, or fullerene, for short, the molecule is the ultimate form of pure carbon. While diamond and graphite consist of only carbon atoms within the crystalline structure, both collect a layer of hydrogen on the surface, attached to loose dangling bonds (1). The fullerene \( C_{60} \) material consists of 60 carbon atoms, and is a spherical molecule consisting of 20 pentagons linking hexagonal rings. The structure exhibits a resonance throughout the molecule and does not readily react with light or air (4).

Another common molecule, fullerene \( C_{70} \), has 70 carbon atoms shaped as an elongated sphere, which spins about its long axis and appears in almost equal quantity. Fullerenes having more than 100 carbon atoms are commonly found, but not at the same quantity of \( C_{60} \) or \( C_{70} \).

The medical industry has proposed uses for the fullerene, counting on its stability to perform specific tasks. Specialized functional groups have been attached to the surface with great success. Hopes are that a fullerene with several functional groups can act like a multiple "lock-and-key" system to perform with several interactive phases with selective enzymes. Should the carbon cage prove to be a sufficient shield, radioactive tracers could be used within the body without danger of affecting living tissue (1).
In the electronics industry, uses have already been explored using the fullerene, which, by the nature of carbon, is a semiconductor. C₆₀ molecules have been found to readily react with a heated silicon surface, (~900-1200 °C), to form a silicon carbide material that is semiconducting at extremes of temperature, power, speed, and frequency. The substance is deposited in spherical domes, arranged in a linear pattern, and is harder and more durable than the presently used silicon dioxide (2).

Recently, scientists have begun encapsulating metallic ions within the carbon shell, whereupon the fullerene takes on the character of the metal. The large array of conjugated π-bonds accepts the donated valence shell electrons, creating a stable ionic entity, and has been tested to the extent where the molecule can be represented as M@+C₆₀ - (7).

Alkali doped molecules exhibit the trait of superconductivity at relatively high temperatures. Using varied dopant materials, the superconductivity can be selectively controlled. A Rubidium-Thallium dopant yields a material that is superconductive at 43K, but degrades upon exposure to air. A formulation of a K₂C₆₀ compound, called Potassium Carbide, which is arranged in a cubic lattice matrix, forms a material that is superconductive at 18K, and is stable in air and light (1).

The area of research is so new, that specific uses have not been implemented. The first big money in this new field will belong to the Chemists and Engineers that develop methods for synthesis and collection of more than gram quantities. Once the bulk material is available on the open market, opportunities for applications in all disciplines of science will be eagerly waiting.

SYNTHESIS

The Curl and Smalley group first synthesized fullerenes by means of laser vaporization of graphite, in a cluster generator device of their own design. A pulsed stream of vaporized carbon material in a gust of helium is carried through a channel where the condensation takes place. It is then ejected through the path of a negative ion detector. Initial yields were enough to resolve samples to perform spectroscopic tests only.

The key to larger yields was found by physicists rather than chemists. Unknown to the Curl and Smalley group, two years earlier, Wolfgang Kratschmer of the Max Planck Institute for Nuclear Physics in Heidelberg, was conducting experiments on light diffraction of interstellar dust which consisted mainly of carbon. They modeled conditions by resistive heating of carbon rods in a helium atmosphere, which is assumed to be found near red dwarf stars. Kratschmer had found a peculiar double humped absorption of U-V light, but filed it away for a later pursuit. After reading of the experiment by the Rice group, Kratschmer repeated his experiment, and in 1990, revealed a better method for the production of fullerenes resulting in much larger quantitative yields, 75% C₆₀, and 23% C₇₀, and what was termed as "a grab bag of larger molecules" (4).
Today, every scientist with an arc welder and a controlled atmosphere device has the capability to produce fullerenes.

Collection of fullerenes is best obtained by means of an electric arc between two carbon rods, under an atmosphere of helium at about ~200 Torr, where the vaporized carbon condenses and is carried in the helium/carbon vapor to where it is cooled and collected. It has been discovered that by heating graphite in an oven to excess of 1200 °C, depositing fullerene material layered on the surface (4). The production of metallofullerenes, a metal ion, encapsulated within the carbon cage, is accomplished by drilling the carbon rods and packing them with powdered metal resulting in a molecule which has a stable ionic charge (6).

Separation of the metallic fullerene is done by HPLC, in a 50/50 mixture of toluene/decalin, where the different species form individual layers. Yields have been low, and the process is time consuming. Some experiments have taken 2 to 3 days to obtain several hundred milligrams (8). New research has shown that porphyrins, large extended ring systems extended from a silica support, much like open hands in a circle, are ion selective, and result in a higher percentage yields of the metallic species (2).

The carbon soot from the arc or laser vaporization method is dissolved in benzene, or a toluene/decalin mixture, and extracted in crystalline form upon evaporation. The crystals can be sublimed under a vacuum while heated at ~400 °C (4).

Since the confirmation of the existence of the fullerene molecule, naturally occurring fullerene material has been successfully extracted from impact crater sites, and in the Cretaceous-Tertiary boundary, where it is presumed to have formed upon impact of large meteorites (3,5).

MECHANICS

The carbon fullerene gives every indication of being a resonant molecule. Examination of the soot from which the fullerene is formed shows that the soot consists of long chains of up to 25 carbon atoms. Held close to the arc by the helium atmosphere, the carbon chains begin to curl up on themselves, and crosslink, forming the stable 5 and 6 membered rings, in a complex structure that connects to itself in even numbered quantities, from 32 atoms to more than a hundred (4). The C_{60} and C_{70} molecules are consistently the most abundant.

NMR tests have shown that each carbon atom in the structure has the same relation to the whole, suggesting the most stable configuration possible, that of a spherical object (4). Tests of the magnetic susceptibility of the fullerene material suggests that the molecule is a weakly bonded van der Waals solid. At ~300 °C the crystalline structure shows a face-centered cubic (fcc) orientation, with a fcc constant of 14.16 A. The C_{60} molecule has an individual radius of 3.53A. Upon cooling, the crystalline lattice changes to a simple-cubic structure, decreasing the fcc constant by 0.044A (6).
The C_{60} molecule has been shown to have two different bond lengths. The five-membered rings have bonds of ~1.40Å, and the six-membered rings have a bond length of ~1.46Å, both of which are shorter than C-C single bonds, 1.54Å, but longer than C=C double bonds, 1.34Å, which aids the resonant theory (6).

The graph on the left, below, is the cluster beam generator sample from the 1985 experiment. On the right, is the U-V absorption spectrum of the Kratschmer vaporization sample from 1990 (4).

Shown below is a graph showing the mass spectroscopy of the carbon/ sulfur sample from the Sudbury impact site showing the C_{60} fullerene having a mass of ~720 amu. The blow-up below, right, shows several peaks around 720 amu, which are accounted for by the formation of fullerenes containing larger isotopes of carbon (3). The peak at ~840 amu is that of C_{70}.
Shown in the graph below, is the mass spectroscopy of the metallofullerene, Y@C_{25}, collected by means of electric arc vaporization of carbon filled rods. Note the abundance of large, empty-cage fullerenes in the sample, showing that separation is difficult manage (7).

CONCLUSION

The field of research involving the synthesis, collection, and application fullerenes brings a new material to begin a new frontier that may accelerate the rate of change of technology, and create an explosion of activity in the science industries. The uniqueness of this molecule is still being researched to be able to understand the ultimate potential in future uses. The carbon fullerene may well be the tool of the future that will build the technology of the 20th Century.
WORKS CITED


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THE SYNTHESIS OF IBUPROFEN

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Abstract

The synthesis of the anti-inflammatory drug Ibuprofen is discussed in its relationship to the nonsteroidal form. In this synthesis, the Arylalkanoic acid is prepared from alkyl aryl ketones by the successive treatment with pyrrolidine, diphenyl phosphorimidate, and potassium hydroxide. Related topics include new methods for the preparation of the more optically and biologically active S(+) enantiomer, and physiological effects on the human body.

Introduction

Ibuprofen, R,S,2-(4-isobutylphenyl) propionic acid, Mp 75-77.5 °, Mol wt 206.27, is known as a nonsteroidal anti-inflammatory agents used in the treatment of arthritis and other similar diseases. It is used as racemic mixture of the two enantiomers S(+) and R(-).

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\begin{align*}
\text{Me}_2\text{CHCH}_2\text{-} & \text{H} & \text{COOH} & \text{S(+) } \\
\text{Me}_2\text{CHCH}_2\text{-} & \text{CH}_3 & \text{COOH} & \text{R(-)}
\end{align*}
\]
The chiral center of ibuprofen is in the propinoic acid moiety. The S-enantiomer is the physiologically active form. It has been shown to be 160 times more potent than the R-enantiomer in inhibiting prostaglandin synthesis. Consequently, there is today an increasing interest in getting a pure enantiomeric form of this therapeutically active drug. However, there is a draw back. Gastrointestinal side effects constitute the most frequent of all the adverse reactions of nonsteroidal anti-inflammatory drugs (NSAIDs). These reactions range in both severity and frequency from relatively mild to the more serious and potentially life-threatening states. It must be stated, however, that Ibuprofen is still less irritative to the stomach and promotes less internal bleeding than does aspirin.

Synthesis

There are many methods for the preparation of Ibuprofen. Many synthetic methods have been proven to show superior yields of the $S(\pm)$ enantiomer, which is in fact the more biologically active compound. However, for our purpose of preparing a nonsteroidal sample of ibuprofen, the synthesis given here is one of the most simple methods known.

4-Isobutylpropiophenone, prepared by the Friedel-crafts acylation of isobutylbenzene with propionyl chloride, was converted to its pyrrolidine enamine, which further reacted with DPPA under argon to give the N-phosphorylated amidine, in 78% yield. Hydrolysis in ethylene glycol gave ibuprofen in 79% yield.
Condensation of alkyl aryl ketones with pyrrolidine smoothly proceeds in refluxing benzene or toluene in the presence of boron trifluoride etherate to give enamines. Addition of DPPA to enamines in tetrahydrofuran (or ethyl acetate), followed by refluxing the reaction mixture, generated nitrogen to yield N-phosphorylated amidines by aryl migration.

Another “one-step” synthesis of ibuprofen involves the use of 2-hydroxypropiophene dimethylacetals using sulfuryl chloride and an amide or a weak base. This is similar to the method stated above, both of which involve aryl-migration.

And, yet, another reaction involves methyl aryl ketones with cyanotrimethylsilane in benzene in the presence of zinc iodide or with chlorotrimethylsilane and potassium cyanide in dimethylformamide, followed by O-acetylation with acetic anhydride in the presence of iron (III) chloride as a catalyst to give the cyanohydrin acetate, deacetoxylation by catalytic hydrogenation to give the corresponding 2-arylpropanenitrile, and alkaline hydrolysis of nitrile to give the 2-arylpropanoic acid.

One of the most interesting synthesis involves a zinc salt catalyzed rearrangement of acetals of optically active aryl 1-chloroethyl ketones to produce optically active (S)-2-(4-isobutylphenyl) propinoic acid. The reaction is shown below.
Carbon-13 NMR Spectroscopy

The NMR of Ibuprofen:

H NMR 7.06 (4H m, aromatic H), 3.67 (1 H, q, CHCH3), 2.29 (2 H, d, CH2),
1.82 (1 H, m, CH(CH3)2).
References

Chapman & Hall.


