Research Work: Accidental, Repetitive or Fundamental?*
In the Light of Benzoin Condensation: Part 1

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Eminent educators, as well as common people, often question why most of the research work is somewhat repetitive and there are very few options for fundamental research in developing science. So, the elementary question is, “what is fundamental research?” Scientific research is driven by an extension of previous research. If we demask the word ‘research’, i.e., ‘further searching’, it obviously leads to repetitive work. But this repetitive work must be driven by some fundamental values of the researcher. In this article, the authors try to address this conflict between repetitive research and fundamental research in light of the never-ending journey of benzoin condensation, which has continued for 150 years. With the help of this example, it can be established that the fundamental outcome of the research can be achieved via a continuous extension of the research process.

1. Introduction

In developing science, research scholars often come across statements such as: In modern India, we have several excellent research institutions like the Universities, IITs, national laboratories, etc. with well-equipped provisions. Still, we are in dire need of much better infrastructural facilities, and we must carry out fundamental research with more difficult problems. Unfortunately, most of us are habituated to working on somewhat repetitive problems that are not at all a part of fundamental research. Such research work is not at all applicable. It is simply for a

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black-white representation in some scientific journals, and this is not accountable for improving our society. And undoubtedly, if we want to be at the cutting edge, we have to be innovators and originators with the concept of fundamental research work.

Such statements are not just made by common people but also by several uninformed scientists and educators.

Now the quite inevitable question is, what do we mean by the term ‘fundamental research’? The answer is: Fundamental research, often addressed as pure research or basic research, refers to the scientific endeavour to advance scientific theories for improved understanding or forecasting of natural or other phenomena. On the contrary, ‘applied research’ uses scientific theories to develop technology or techniques to mediate and modify natural or other phenomena. One can easily say that fundamental research fuels applied science’s innovations, and both of them are interconnected with development.

In this connection, it may be informed that selecting a topic can be the most challenging part of a research assignment. Usually, in most cases, our instructor will give us a rough guideline as to what can be the research question and what we can do to execute the research work. If we think appropriately, it will be apparent that the instructor’s guidelines originate from his/her research guide. However, in some cases, a topic of personal interest is selected. However, such personal interests are not abrupt but originate from some unexpected observations during studies on routine work. Once we have identified the topic, a literature survey becomes necessary. After a proper and elaborate literature survey, we get the direction of our research work. Failure to work within these guidelines may also result. But this failure will again direct the proper pathway to carry out the research. Evidently, then research work is undoubtedly repetitive work. An appropriate analysis of the word ‘research’, which means ‘further searching’, also indicates so. In addition, we think it is better to say that ‘research’ is simply for the sake of ‘research’ and whether it is the so-called fundamental or not does not matter. However, a scientific researcher is prompted by a driving inquisitiveness about the
unknown, which is undoubtedly an extension of previous research work. Discovery of truth and understanding of nature are her/his objectives. A researcher’s professional reputation depends upon the originality and soundness of the work. The individuality and creativity of the researcher are usually stamped on each of her/his efforts, just as an artist’s style is apparent in her/his work.

Let us look closer at the never-ending journey of ‘benzoin condensation’, which began in 1824. The cyanide-catalysed benzoin condensation was first reported as early as 1824 by Carl Heinrich Strange [1], and since then, it has been the subject of many investigations. Benzoin condensation was then described in 1832 [2] by Justus von Liebig and Friedrich Wöhler during their research on bitter almond oil. The catalytic version of the reaction involving cyanide was later developed by Nikolay Nikolaevich Zinin in the late 1830s [3]. Thus, the journey of benzoin condensation began, and the research on this topic is still ongoing. Let us try to track this journey sequentially, in short, and authorise the scientists and educators to judge whether it is repetitive or fundamental research.

2. The Beginning: Is it an Accident?

As we mentioned, Strange (in 1824) [1] first reported about the cyanide-catalysed benzoin condensation in *Buch. Rep. Pharm.* But such an early paper is not available in the archives, so it becomes quite impossible to discuss his study. However, during their research on bitter almond oil in 1832, Justus von Liebig and Friedrich Wöhler described benzoin condensation [2]. The two names, Justus von Liebig and Friedrich Wöhler, have their own signature marks in the world of chemistry and are considered the principal founders of organic chemistry. Justus von Liebig established the first laboratory for experimental chemistry where qualitative and quantitative analysis followed by organic preparations were taught systematically. Soon this experimental laboratory became well recognised, and students began to flock to his laboratory from all parts of Europe, among whom some turned out to
Figure 1. Structures of cyanic acid and fulminic acid.

be notable scientists of the next generation. Liebig’s own investigations covered a wide range of interests, and one of his most famous collaborators was Friedrich Wöhler. The friendship between Liebig and Wöhler grew stronger (in 1825) after they amiably resolved a dispute over two substances, i.e., cyanic acid and fulminic acid, that apparently had the same composition but very different characteristic features. The silver compound of fulminic acid, investigated by Liebig, was explosive in nature, whereas silver cyanate, as Wöhler found, was quite stable. In this context, let us have a look at the structures of cyanic acid and fulminic acid [4] (Figure 1).

Let us have a look at the starting point of their research on bitter almond oil, where they described benzoin condensation. In June 1832, Liebig learned that Wöhler’s first wife passed away soon after giving birth to their child. He wrote a noble letter (15 June 1832) of consolation to his friend [5] (see Box 1).

From this tragedy emerged one of the most important collaborative papers in the history of chemistry. Liebig and Wöhler were not the first chemists or pharmacists to have investigated the composition of bitter almonds. When they began their research, the status of knowledge on this topic was as follows: In 1823, the German pharmacist Carl Heinrich Strange identified the crystals formed from the aerial oxidation of oil of bitter almonds as benzoic acid [1]; he also extracted the same from the cherry laurel. In France, Pierre Robiquet [6] also extracted a crystalline nitrogenous material called amygdalin from the almond nut, which was
also known to contain a poison called prussic acid. He found out
that sweet almonds didn’t contain amygdalin; when oxidized with
nitric acid, amygdalin gave benzoic acid. Amygdalin, with water,
gave no smell of bitter almonds. (Here, a point to be noted is that
prussic acid is hydrogen cyanide.)

**Box 1. Letter From Liebig to Wöhler**

“My poor dear Wöhler, who could have predicted such a dreadful misfortune after so happy a confinement; how empty are the words of consolation after such a loss. I cannot tell you; I cannot express the feelings I had on receiving the news; it was as if I had actually experienced loss myself. When I think to myself how satisfied and lucky you were in your domestic arrangements and of the affection and love you had for one another, and now this shocking dismemberment of all your hopes, this foundering of all your wishes! The good wife, so young, so full of life and goodness, and for her parents and yourself so irreparable. Come to us, dear Wöhler if we can provide any consolation and help to heal your grief. To stay in Cassel at such a time will be injurious to your health. We can busy ourselves with something. I have bought some amygdalin from Paris [from Pelouze] and I shall have some 25 pounds of bitter almonds to work on. You must not travel, you must get occupied, but not in Cassel. I feel your distress will disappear in work and, it will also
be better if your sorrow is shared with a friend…come to us; I expect you by the end of the week.”

Liebig and Wöhler obtained the almond oil in a much purified
form through a rigorous distillation process, and they relied on
consistent specific gravity readings as a criterion of purity as its
boiling point (179°C) was beyond the reach of the graduated scale
of the thermometer used in those times. The crude almond oil
was supplied to them by Gay-Lussac’s favourite student Jules
Theophile Pelouze [5]. This purified oil was later verified to
be benzaldehyde. When they dissolved amygdalin in water and
treated it with crushed or emulsified sweet almonds, it yielded
the oil of bitter almonds. But when the mixture was allowed
to boil, it coagulated and didn’t form the oil of bitter almonds.
They investigated the structure of benzaldehyde while treating it
with a series of chemical reactions; and found out that the central
‘core’ of the molecule remained intact. Thus their studies on bit-
ter almond oil further established the idea that certain groups of
atoms—what they called—‘radicals’ (what we might call ‘reac-

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Scheme 1. Fermentation of amygdalin.

tive groups’ or ‘functional units’) might be transmitted unchanged through chemical transformations (in this case, the benzoyl group in benzaldehyde, benzoic acid, benzoyl halides, benzamide) and these units, such as the benzoyl unit could be used to explain a whole range of chemical reactions and the molecules formed from them. This opened the door for organic structure determinations.

According to modern science [7], amygdalin is decomposed by a ferment (an enzyme) present both in sweet and bitter almonds (but not in the boiled emulsion of almonds!), and besides oil of bitter almonds and prussic acid, grape sugar is formed (Scheme 1).

Amygdalin was the first example of a glycoside. Wöhler and Liebig recognized that the action of the ferment, which they called emulsin, was similar to that of yeast on sugar (which Berzelius has attributed to a peculiar, catalytic force). In this context, it may be mentioned that amygdalin is classified as a cyanogenic glycoside because each amygdalin molecule includes a nitrile group, which can be released as the toxic cyanide anion by the action of a $\beta$-glucosidase. Eating amygdalin will cause it to release cyanide in the human body and may lead to cyanide poisoning.

In 1832, F. L. Winckler [8] found that crude oil of bitter almonds, containing hydrocyanic acid with hydrochloric acid, forms a new acid called mandelic acid. In a note (1836), Liebig suggested that the hydrocyanic acid is hydrolysed into ammonia and formic
Scheme 2. Generation of mandelic acid.

Scheme 3. Mandelic acid from amygdalin.

acid, which combines with the benzaldehyde to yield mandelic acid (Scheme 2).

Strictly speaking, mandelic acid is formed from amygdalin through the acid-catalysed hydrolysis of the glycoside to yield glucose and cyanohydrin of benzaldehyde followed by the acid catalysed hydrolysis of the said cyanohydrin (Scheme 3).

In this connection, it may be mentioned that mandelic acid is found in almonds, and its name is derived from the German word for almond—Mandel.

The formation of benzyl alcohol by the action of alcoholic potash on the oil of bitter almond was noticed by Wöhler and Liebig [2], but its true nature was first established by Cannizzaro. This is thus

The formation of benzyl alcohol by the action of alcoholic potash on the oil of bitter almond was noticed by Wöhler and Liebig, but its true nature was first established by Cannizzaro.
Scheme 4. Cannizzaro reaction in 1853.

A disproportionation reaction which was first reported by Cannizzaro in 1853 [9] when he obtained benzyl alcohol and potassium benzoate from the treatment of benzaldehyde with potash (Scheme 4).

As mentioned earlier, benzoin had been observed by Robiquet [6], but it was first correctly examined by Wöhler and Liebig [2]. They obtained it by the action of alkali on benzaldehyde (oil of bitter almond having molecular formula C₇H₆O) and found by analysis that benzoin (having molecular formula C₁₄H₁₂O₂) is isomeric with benzaldehyde. In this context, it may be informed that molecular formulae are given in accordance with modern science. Nikolay Nikolaevich Zinin, on the advice of Liebig [10], was working on the synthesis of benzoin, and in the late 1830s, first showed that its formation depends on the presence of hydrocyanic acid [3] in the oil of bitter almonds and that the catalyst for the reaction is potassium cyanide.

Let us discuss Nikolay Nikolaevich Zinin [11] and his study on benzoin condensation [3]. The rise to eminence of the chemistry school at Kazan can usually be traced back to Nikolay Nikolaevich Zinin. Although his colleague at Kazan, Karl Karlovich Klaus, may have played an equally important part in its development. After graduating with a degree in physics and mathematics, Zinin was appointed as adjunct of those disciplines. However, the Ministry of Education had other plans for the young man. Despite his lack of knowledge in chemistry, he was appointed to teach chemistry after the dismissal of the ‘undistinguished’ professor of chemistry, Dunaev. It was common practice at that time for professors to be appointed to lecture students in the requi-
Scheme 5. Benzoin condensation reported by Nikolay Zinin.

site subjects without necessarily considering the qualifications of the instructor in the subject. As part of his training for the professoriate, Zinin was sent on a study leave abroad to attend lectures by eminent western chemists. This was not intended as a research trip, but Zinin nevertheless spent time in the Giessen laboratory of Justus von Liebig, where he established the benzoin condensation [3]. How this reaction was established is not known, but it was a well-known fact at that time that the condensation of benzaldehyde to benzoin was catalysed by cyanide anion. It is also known that Zinin was in Liebig’s laboratory when Liebig and Wöhler were carrying out their seminal research on benzoyl compounds. The synthesis of mandelonitrile (benzaldehyde cyanohydrin) by slow addition of hydrogen cyanide to benzaldehyde failed to give the desired product. So, under certain conditions, when the cyanide salt was added to the aldehyde too slowly or when insufficient amounts of cyanide (catalyst) were used, the product isolated from the reaction turned out to be benzoin. Thus, the optimised reaction condition was when benzaldehyde was refluxed with aqueous ethanolic KCN; benzoin was formed (Scheme 5).

Zinin presented his research results at the University of Saint Petersburg, a Russian federal state-owned higher education institution from where he received his PhD. Another piece of information worth mentioning is that in St. Petersburg, Zinin was a private chemistry teacher to the young Alfred Nobel and left for the University of Saint Petersburg in 1841. However, is it possi-
ble that Zinin’s experimental technique was expected to remain in the embryonic stage due to lack of experience and that it later led to the discovery of a new reaction? Our experience in organic synthesis leads us to believe so, but this cannot be proven beyond doubt. On his return to Kazan in 1841, Zinin became increasingly interested in organic compounds. His work on benzaldehyde and benzoin could not continue as the import of the poisonous oil of bitter almonds was prohibited by Russian customs regulations. As a result, he began studies with nitro-aromatic compounds [12] that led to the monumental discovery of the reduction of nitroaromatic compounds to anilines and the synthesis of azobenzene, azoxybenzene, and benzidine. Now there are two questions:

- Firstly, in 1823, from where did Carl Heinrich Strange get the idea to study the oil of bitter almonds?
- Secondly, from where did Justus von Liebig (in 1832) get the idea to conduct research on bitter almonds?

There isn’t very vivid information or answers to these queries. Hence, can it be concluded that both of these ideas found their way back to continued research from the laboratory of Joseph-Louis Gay-Lussac in Paris? This appears to be, to some extent, logical, as we had pointed out that almond oil was supplied by Gay-Lussac’s favourite student Jules Theophile Pelouze [5]. If this is so, then it appears that Justus von Liebig and Friedrich Wöhler might have started their research on bitter almonds by taking the lead from their research guide. However, undoubtedly, it is known [11] that Nikolay Nikolaevich Zinin was advised to study bitter almonds, or rather benzoin condensation by Justus von Liebig. Again, with Liebig’s recommendation, Zinin [11] went to Paris, where he attended the lectures of luminaries of chemistry such as Jean-Baptiste-André Dumas and Joseph-Louis Gay-Lussac. Note that Zinin had a close association with Joseph-Louis Gay-Lussac in Paris while working in the laboratory of Jules Theophile Pelouze (who was also a close associate of Liebig). Thus, although it is unclear from where the studies on bitter almonds originated, it is fair enough to conclude that
3. Establishment of the Mechanism of Benzoin Condensation: Arthur Lapworth’s Breakthrough!

The observation that readily converted benzaldehyde into benzoin using potassium cyanide was first made by Zinin in 1840 [3]. However, the details of the method as practised were described by Ernst Carl Theodor Zincke only in 1879 [13]. Notably, since the first result, 40 years had elapsed before developing the exact experimental method to obtain benzoin from benzaldehyde. In 1882, Hermann Emil Louis Fischer [14], German chemist and 1902 recipient of the Nobel Prize in Chemistry, along with Hans V. Neyman extended it to the condensation of furfural to furoin (Scheme 6).

![Scheme 6. Benzoin condensation of furfural in 1882.](image)

Of the various theories which have been put forward pertaining to the mechanism of the reaction, the theory proposed by Ernst Carl Theodor Zincke in 1879 [13] and Chalanay and Knoevenagel [15] were the first ones to come up with a plausible mechanistic pathway. Zincke assumed that mandelonitrile was formed as an intermediate product and that this, reacting with unchanged benzaldehyde, with the elimination of hydrogen cyanide, yielded benzoin (Scheme 7).
Scheme 7. First proposed plausible mechanism of Benzoin condensation in 1879.

Scheme 8. Proposed plausible mechanism in 1892.

Evidently, it is a simple representation and not in accordance with modern science’s mechanistic details. At the same time, it was found that benzaldehyde and hydrocyanic acid did not react to give benzoin; the aqueous solution of KCN is alkaline in nature. In this context, it may be noted that the theory of Chalanay and Knoevenagel proposed in 1892 [15] is well-known. They suggested that a potassium derivative of benzaldehyde and mandelonitrile was formed in the first instance, and this subsequently reacted (Scheme 8).

But the existence of this potassium compound was purely hypothetical, as neither a compound of this kind had been isolated, nor was there any indirect evidence that the hydrogen atom assumed to be replaced by potassium was reactive in the presence of alkali.

Then appeared Arthur Lapworth’s work on divulging the mechanistic course of benzoin condensation [16]. Arthur Lapworth was one of the first, if not the first, organic chemists to present his findings from a contemporary mechanistic perspective. In at-
Box 2. Sir Robert Robinson on Arthur Lapworth (in 1974)

“He contributed in particular, a series of fundamental observations which workers in various parts of the world have expanded into whole fields of investigation, and amongst the mass of information, which was organic chemistry, he picked out certain laws, at first of quite limited application, which he and others have been able to fuse into more general principles of great scientific significance.”

Scheme 9. Loss of colour of yellow camphor quinone with time.

tempting to evaluate the beginnings of the mechanistic view not only of benzoin condensation but also of organic reactions, the contribution of Arthur Lapworth deserves a considerable degree of appreciation. Sir Robert Robinson, British organic chemist and Nobel laureate recognized in 1947, has written about Arthur Lapworth [17] (see Box 2).

Lapworth’s most fantastic achievement in elucidating reaction mechanisms dealt with transformations associated with carbonyl compounds. In his mechanistic studies, Lapworth constantly applied novel approaches using kinetic methods wherever possible. Thus, in the pioneering study of the rate of cyanohydrins formation from carbonyl compounds in 1903 [17], he studied the loss of colour of yellow camphor quinone with time as shown in Scheme 9.
Scheme 10. Lapworth’s proposal for the formation of ionic complex.

Scheme 11. Protonation of ionic intermediate to generate cyanohydrin.

Assuming that the reaction was ionic in nature and reversible, Lapworth proposed that the carbonyl group was polarized because of the ‘residual affinity’ of oxygen and thus reacted with cyanide ion to form an ionic complex which may also follow the reverse course (Scheme 10).

According to the kinetic evidence, the second step of the reaction must be a rapid reaction of the ion with a proton source such as water, alcohol, or an acid (Scheme 11).

In order to prove that the initial complex of carbonyl compound and cyanide was a stable entity, Lapworth, in 1904, studied various carbonyl compounds with an excess of KCN [16] and isolated compounds that had the composition representing the composition of ‘a hydrated potassium salt of the corresponding cyanohydrins’.

Now, it was only a small jump to extend this elegant explanation of cyanohydrin formation to benzoin condensation. Arthur Lapworth and Reginald W. L. Clarke [18] proclaimed in 1907 that
Scheme 12. The mechanistic course of benzoin condensation proposed by Arthur Lapworth.

benzoin condensation is of special interest, firstly, because potassium cyanide plays the part of a true catalytic agent, being practically unaltered in the amount at the end of the operation and required to be used only in relatively small quantities, and secondly, because it is not applicable to the aldehydes of the fatty series. Lapworth argued that adding the elements of hydrogen cyanide to benzaldehyde would produce mandelonitrile. The mechanistic course of benzoin condensation as proposed by Arthur Lapworth [18] with slight modification in accordance with modern science is as shown in Scheme 12.

The enhancement of acidity and labiality of the methine hydrogen between cyanide and an aromatic nucleus was recognized as the key to the reaction and thus explained why the condensation could not proceed without this anion. To prove this hypothesis, Arthur Lapworth put forward several pieces of information along with some experimental observations [18], as follows:

- In 1903 he pointed out that (and it is now generally accepted) the condensation of ketones and aldehydes with compounds such as ethyl malonate, acetoacetate, benzyl cyanide, and in general, 

1 Easily broken bonds.

The enhancement of acidity and labiality of the methine hydrogen between cyanide and an aromatic nucleus was recognized as the key to the reaction and thus explained why the condensation could not proceed without this anion.
Scheme 13. Formation of hydroxy compound in an additive process.


such substances is the result of an additive process in which a hydroxy-compound is produced, as in Scheme 13.

Now it has been shown that the first product of the action of potassium cyanide on benzaldehyde is mandelonitrile. The former, like benzyl cyanide itself, has a labile $\alpha$-hydrogen atom and, in the alkaline solution, would condense with benzaldehyde as in Scheme 14, which is simply the unstable cyanohydrin of benzoin. This would break up reversibly into benzoin and hydrogen cyanide, which would then be available for further conversion of the benzaldehyde. To test this view, Lapworth placed mandelonitrile, benzaldehyde, and tripropylamine in contact for 20 days and isolated a quantity of benzoin.

The kinetics of the benzoin reaction, as determined by Bredig and Stern [19], confirmed Lapworth’s predictions. Lapworth put forward this information in 1907 [18] as mentioned in Box 3.

- Arthur Lapworth was well aware of the fact that $\alpha,\beta$-unsaturated carbonyl compounds are susceptible to conjugate addition. Thus Lapworth proposed that mandelonitrile might be expected to react
Box 3. Kinetic Confirmation of Lapworth’s Prediction

“Sometime after these suggestions were published, a communication from Bredig and Stern appeared in 1904. They described experiments on the velocity of the benzoin condensation and were able fully to establish that the reaction is brought about catalytically by the potassium cyanide, the velocity being directly proportional to the concentration of the cyanogen ion in all cases.”

Scheme 15. Proposed reaction of mandelonitrile with α,β-unsaturated ketones.

with α,β-unsaturated ketones (Scheme 15).

This is the same cyanohydrin of a δ-diketone, in which the product is obtained by eliminating hydrogen cyanide, as in the benzoin condensation itself. According to Lapworth, the product from mandelonitrile and α,β-unsaturated ketones were too unstable, and decomposition took place. It was therefore decided to employ a nitrile derivative, less easily affected by alkalis but of analogous structure. Thus, Lapworth used the aniline derivative, namely, the compound obtained by combining hydrogen cyanide with benzylideneaniline (Figure 2) and carried out the reaction with carvone as the unsaturated ketone and desired the phenylimino-derivative of β-benzoyldihydrocarvone being produced (Scheme 16).

The new substance is easily hydrolysed by acids to yield aniline and two stereoisomeric (diastereoisomeric) benzoyldihydrocarvones. Thus, it absorbs only one molecular proportion of bromine, showing that it now contains only the carbon-carbon double linking in the isopropenyl group. It shows the phenomenon of mutarotation in the presence of traces of alkalis, indicating that it
**Figure 2.** The compound obtained by combining hydrogen cyanide with benzylideneaniline; the reaction carried out with carvone as the unsaturated ketone. The desired phenylimino-derivative of β-benzoyldihydrocarvone is produced (*Scheme 16*).

![Chemical structure](image)

**Scheme 16. Reaction of carvone as unsaturated ketone.**

contains the carbonyl group attached to an asymmetric centre, not present in the original carvone. Further, only one molecular proportion of hydroxylamine combined to give an oxime derivative, and its dioxyine was finally isolated by the indirect process of treating the original phenylimino-compound with hydroxylamine acetate. Undoubtedly, it is a nice piece of research work, even by modern standards. At the same time, it may be informed that this work is the origin of the Stetter reaction, which will be discussed in the next part of the article.

4. In Closing...

Summing up our discussions so far, we may have the impression that there is enough on benzoin condensation as the proper method for preparation of benzoins and its mechanistic course is firmly established. Hence, anyone is unlikely to conduct further
research in this field! However, the findings from any study carried out in a proper direction are simply that of the researcher and are always prone to (and need) additional interpretation. We will continue to study this area further in the second part of the article. It will be revealed that improved results are the consequence of a continuous research process.

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