



Citation: F. Naso (2017) Mario Betti: a Giant in the Chemistry Scenario of the Twentieth Century. *Substantia* 1(2): 111-121. doi: 10.13128/substantia-31

Copyright: © 2017 F. Naso. This is an open access, peer-reviewed article published by Firenze University Press (<http://www.fupress.com/substantia>) and distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Competing Interests: The author declared that no competing interests exist.

Historical Article

Mario Betti: a Giant in the Chemistry Scenario of the Twentieth Century

FRANCESCO NASO

Synchimia srl, Spin Off University of Bari, Italy, Dipartimento di Chimica, Via Orabona, 4, 70126, Bari

E-mail: francesco.naso@uniba.it

Abstract. The life of the chemist Mario Betti (1875-1942) is presented by focusing on the activity performed at the University of several Italian cities. Born in Bagni di Lucca, a small town in Tuscany, in 1897 he graduated in chemistry at the University of Pisa, under the supervision of Roberto Schiff, nephew of the famous Ugo. In 1900, he moved to the University of Florence, where he published a three component reaction which became known world-wide as *the Betti reaction* and, nowadays, represents a synthetic tool of increasing use. The product deriving from the reaction can be easily obtained optically resolved and used as ligand in catalysts of nucleophilic attack on carbonyl compounds. Since then, stereochemistry was the subject in which the most relevant achievements of the Italian chemist were made. After working in Florence, Betti spent a ten years long period at the University of Siena, where he covered the role of faculty dean and rector. In 1922 he was hired by the University of Bologna as successor of the famous Giacomo Ciamician. In this article the many merits of this open minded and farsighted man will be presented against a background with chemistry and chemists of the 20th century playing on the scene. The conclusion is reached that the chemical heritage of Mario Betti, after a long time from his death, appears richer than previously thought.

Keywords. Betti reaction, Betti base, Mannich reaction, chirality, asymmetric synthesis.

1. INTRODUCTION

Chirality (the existence of a couple of compounds that are non-superimposable mirror images, *i.e.* enantiomers) is a wide topic of paramount importance in chemistry. Several features of interest concerning this type of stereoisomers, and, especially, the maniacal preference shown by mother nature towards one of them, are still unclear. The chemist-writer Primo Levi was attracted by this “beautiful and fertile”¹ theme ever since he started to prepare his degree thesis on the stereochemical problems connected with the Walden inversion.² Later on, after becoming very famous for his literary masterpieces, he wrote an article where his enthusiasm for the enigmatic subject appears unchanged.¹ As for me, stereochemistry, including chirality, was one of the areas in which I enjoyed working since the early stages of my

scientific career. During this activity, reading literature papers I met the name of Mario Betti and eagerly studied his work, thus becoming aware of the importance of his ideas and achievements. At the same time, I got convinced that the scientific potential generated by the Betti's chemistry was far from being fully developed. As a consequence, my dedicated co-workers and myself decided to embark on a journey with the aim of expanding the Betti's chemistry and to use it as a tool for developing our interest in stereochemistry.^{3,4} Furthermore, we wrote a review⁵ in order to increase further the attention towards the work of the Italian scientist. The present contribution, that is mainly of biographical nature, aims to go in the same direction, hopefully, with the same success.

2. MARIO BETTI: THE LIFE⁶⁻¹⁰

2.1 *The Betti Family and the Pharmacy in Bagni di Lucca: Music and Drugs*^{6,7}

Mario Betti and his twin brother, Adolfo, were born in Bagni di Lucca on March 21, 1875 from Adelson and Dalmanzina Amadei. Bagni di Lucca is a small town in Tuscany, situated about 60 miles northwest of Florence. The town is rather well known for its thermal baths, that attract visitors from Italy and foreign countries. It seems also worth noting that the celebrated chemist Davy visited frequently the town with the aim of studying some hydrological problems. Adelson Betti was a chemist who owned an antique pharmacy, that had been established in 1709 and, after being run by generations of descendants of the first owners (the Ghiareschi's), in 1833 was inherited by Adriano Betti, son of Ippolito and Maria Teresa Ghiareschi. Along the years, the place reached a high level of professionalism and attractiveness, also due to an uncommon library endowed with rare books. The pharmacy was also known by the inhabitants of Bagni di Lucca as "the English pharmacy". The unusual adjective derived from the fact that around 1870 the pharmacy was awarded by the Queen Victoria the title of "Pharmacy of the British Embassy", with the right of using the royal English coat of arms.

Adelson Betti, son of Adriano, was the subsequent owner of the pharmacy. Being fond of music, he used to play organ in the Bagni di Lucca church. Often, another young musician was playing there and the same man was frequently welcome as a guest at the Betti house, located at the upper level of the pharmacy. One may imagine a place enveloped within a cloud of dream melodies, especially upon hearing that the young musician was Giacomo Puccini (1858-1924). The excellent

hospitality of the Betti's was reciprocated by Puccini who, gladly accepting an Adelson request, composed the hymn *Vexilla regis* for the local church. This musical background greatly influenced the two Adelson's twins. One of them, Adolfo, after studying in Italy and Belgium, became a famous violinist, teacher and music editor. In particular, he is known for having led for years (1923-1929), as a first violinist, the Flonzaley Quartet. The ensemble, that was considered as the earliest top-notch American string quartet, gave approximately 2500 performances in the United States and another 500 in Europe. When the quartet disbanded, Adolfo Betti taught music in New York for several years, receiving in 1933 the Coolidge Medal for eminent services to chamber music in the United States. Later on, he returned to Italy, becoming the mayor of Bagni di Lucca at the end of World War II. Adolfo Betti died on December 2, 1950.^{7,11,12}

The twin brother Mario was also culturally inclined towards humanities, especially music and painting. However, he was afflicted by deforming arthritis and, on the other side, his presence in the pharmacy was badly needed by his father. At the time a pharmacy located in a small town represented an aggregation centre for the most important cultured men of the place. Discussions on politics, social problems and other topics went on with a high frequency. This sort of cenacle was beneficial for the formation of the young Mario. Needless to say, a pharmaceutical path was planned for him.

2.2 *The Pisa Period*^{9,13}

In 1892 Mario Betti registered as a student at the Chemistry School of the University of Pisa. The school had a high reputation, thanks also to the presence in previous times of well known chemists, such as Raffaele Piria (1814-1865), Stanislao Cannizzaro (1826-1910) and Cesare Bertagnini (1827-1857).

At the beginning, Betti chose to follow the course that, eventually, would have allowed him to obtain the "Diploma in Farmacia", that he needed to direct a pharmacy and, as a result, a quiet future in Bagni di Lucca was easily predicted. However, after the first year, the university student realised that his growing interest in chemistry could have been hardly satisfied upon reaching this target. Therefore, he changed his plans by asking to the faculty to be transferred to the second year of the course in Chemistry and Pharmaceutical Sciences. The faculty was very reluctant to express the necessary opinion in favour and the transfer procedure stopped at a dead end. The young student, who had plenty of drive, decided to grasp the net-

tle by lodging complaints in a letter addressed directly to the Minister of Education in Rome, who happily solved the problem within a short time.

Most frequently, the research performed at the Institute of Pharmaceutical Chemistry of Pisa dealt with synthesis and behaviour of heterocyclic compounds or with relationship between structure and physical properties. At the same institute Betti became a pupil of Roberto Schiff (1854-1940), son of the famous physiologist Maurizio (1823-1896) and nephew of the great chemist Ugo (1834-1915). The Betti's supervisor was of high intellectual level, but unhappy with his teaching duties (pharmaceutical chemistry), that he never liked. Roberto felt much more attracted by the passion of collecting artworks, a field in which he had a rare expertise, luckily associated to a large availability of money deriving from his marriage with Matilde Giorgini (1860-1940), a rich girl who was a granddaughter of Alessandro Manzoni (1785-1873), one of the most famous Italian writers and poets of all time. In spite of this distraction, Roberto was able to establish with his student a fruitful co-operation, in which his fanciful ideas were driven into the real world by the experiments of the younger co-worker.^{9,13} In 1897, Betti obtained his degree with a thesis on the reaction of methylisoxazolones with aldehydes and co-authored with Roberto Schiff the first two papers of his career.^{14,15,16}

2.3 The Florence Period

In 1898, Betti moved to the University of Florence as an assistant of Ugo Schiff, who was founder and director of the Institute of Chemistry. The famous chemist, well known for his bad tempered character, was not adequately friendly with his colleagues and showed a severe behaviour towards his students. A few anecdotes will suffice to understand the man.

When a student started to work towards his thesis in the lab, Schiff was used to play always the same scene. He gave to the student a low quality match box warning him with these words:

You must keep in mind that you descend from Berzelius because Berzelius taught chemistry to the old Wöhler and the old Wöhler taught chemistry to me. A school can be honoured by its pupils, but it may be also stained: think it over.^{9,13}

Schiff was a follower of the classic approach to organic chemistry without any enthusiasm towards physical chemistry "interferences". With his caustic style he liked to express the following opinion:

*One day some chemists lost their wish of working and for this reason they invented physical chemistry.*⁹

The Schiff's behaviour towards people of other disciplines was even more drastic. In 1879 the physicists and the chemists of the University of Florence had to move to the same building. Once they had moved there, Schiff got in contrast with the physicist Antonio Roiti (1843-1921), an expert of electrology, who had to run his experiments during the night, due to the interferences caused by the trams passing in the neighbourhood during the daytime. At night, with the aim of disturbing the experiments of his colleague, Schiff enjoyed moving metallic masses in the corridors of his floor located below the level of the physicist labs.¹³

The chemist Augusto Piccini (1854-1905), who in 1893 was professor of pharmaceutical chemistry in Florence, is considered the author of a witty classification of the Schiff family group. Such a classification, related with oxidation state of the elements and nomenclature, required the definition of *schiffico* for Maurizio, *schifoso* for Ugo, and *iposchifoso* for Roberto. Even without inventing an English translation of these terms, the tricky joke is easily understood by taking into account that *schifoso* in Italian means *nasty*.^{9,17}

These funny tales have been reported here with the intention of emphasising the difficulties that Betti expected when he entered the Institute of Chemistry in Florence. He was going to face a supervisor who had a diametrically opposite character. Fortunately, a miracle occurred because the two men shared the high sense of

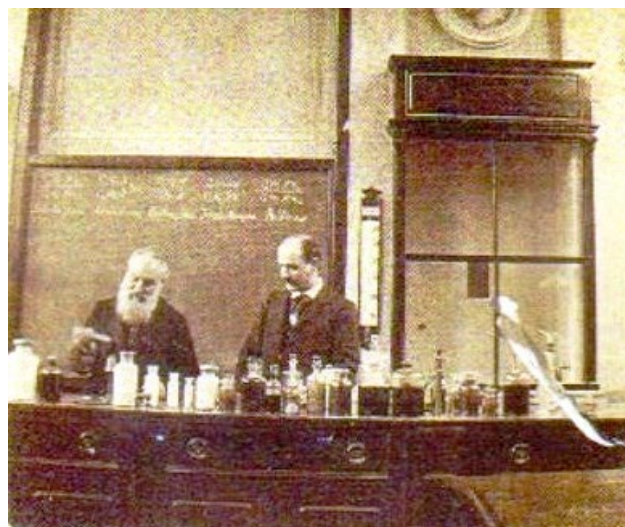


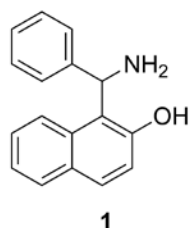
Figure 1. Ugo Schiff and Mario Betti during a lecture in a classroom (Courtesy of "Ugo Schiff" Chemistry Department of Florence University. Chemical Heritage Project DCO155).

duty and the passion towards research. This was sufficient to establish the character compatibility needed. The driving forces towards a fruitful coexistence were strengthened by the fact that the behaviour of the younger scientist was paved with a constant serenity, a convincing reasoning, and a kind way of acting.

After a short time, due to a simple incident, Schiff was obliged to take a long sick leave, during which Betti became responsible for all research and teaching activities. On his return, Ugo Schiff deeply appreciated the work that had been made by his worthily substitute. His hearth became less hard, since he realised that, after all, his co-worker was inspired by the same ideals.⁹

On the other hand, the chemistry environment was very sparkly and this had a beneficial effect on the scientific productivity. In the Florence laboratories, Betti developed his interests in stereochemistry with important studies on the relationship between optical rotatory power and the structure of groups connected with the stereocentre.¹⁸ On performing these studies, a great advantage was achieved by the synthetic versatility of the reaction, nowadays known as the Betti reaction, that in the original version produced 1-(α -aminobenzyl)-2-naphthol **1** (scheme 1), starting with 2-naphthol, benzaldehyde, and ammonia.^{19a} The product begun to be known with the name of the author (*i.e.* Betti base, **1**) and the multi-component process was published in *Organic Syntheses*,^{19b} a prestigious international book series, where only independently checked synthetic procedures are reported. Finally, the base was also easily resolved into his optical isomers by means of tartaric acid.

Meanwhile, Betti had gained high scientific reputation. The Italian chemistry community had a clear sign that a new shining star was rising in Italy during an important meeting held in Parma (*i.e.* Congresso della Società per il Progresso delle Scienze, September 27, 1907). Betti gave a speech on his research in a session chaired by Emanuele Paternò (1847-1935). At the end of the talk, the great chemist Giacomo Ciamician (1857-1922) expressed his enthusiasm and appreciation to the speaker in front of the audience.^{8,9}



Scheme 1. Structure of 1-(α -aminobenzyl)-2-naphthol.

2.4 The Siena Period

In the same year Betti won a public selection for the chair of Pharmaceutical Chemistry in Cagliari, where he worked two years and founded the Institute of Pharmaceutical Chemistry. At the end of his stay in Sardinia, another public selection led him to the University of Siena. The time spent in this University was ten years long and fruitful and Betti kept forever pleasant memories of this period. His professional experience was enriched by highly qualified management roles. Indeed, he became first dean of the Faculty of Sciences and afterwards, at the age of forty, the youngest rector in Italy.

2.5 The Bologna Period

Two subsequent competitive examinations occurred in the Betti life. In 1921 he became professor at the University of Genoa. In this city he met a young chemist who appeared to him very eager to explore the exciting world of molecules. Giovanni Battista Bonino (1899-1985), this was the name of the enthusiastic fellow, impressed professor Betti to such an extent that within a couple of weeks the young chemist was called to cover a temporary position as a technician at the university, in view of a more rewarding research oriented job.

In January 2, 1922, Giacomo Ciamician died in Bologna. The top level University, to which the famous chemist had contributed his highly qualified chemistry, stimulated the interest of many Italian professors, who were eager to move to Bologna. The success at the competition appeared soon an up-hill task. The Italian term for “public competition” is “concorso”, but people of the community invented a whimsical neologism by making the “absolute superlative” of *concorso*, *i.e.* *concorsissimo*, and, besides this grammatically amusing term, nothing appeared more appropriate to convey to the interested people the idea of “the most difficult public competition of the century”.⁶ Eventually, a prestigious *ad hoc* committee was formed. The group included authoritative chemistry professors, such as Nicola Parravano (1883-1938) and Guido Pellizzari (1858-1938). The merits of each of the many applicants were scrutinised and Mario Betti was unanimously selected.⁶

Meanwhile, a new building was ready to host the chemists of the University of Bologna. The direction of the new institute was entrusted to Betti, who had to face financial problems that appeared exceedingly severe. Updated instrumentation as well as furniture for the wide space were badly needed. On the other hand, the money granted was not sufficient even for the basic activity of the structure. The university fund that was

allotted each year amounted to 25,000 Italian lire, a sum that, converted in today value, should roughly corresponds to 20,000 euro. Nevertheless, Betti undertook the uphill task and was able to give the start to the institute, that was called “Istituto di Chimica Giacomo Ciamician” to honour the great chemist, who had made well known world-wide the top level chemistry performed at the university.

During the early years of his stay in Bologna, Betti started to show his deep interest in the relation between *in vitro* chemical reactions and biochemical transformations. He realised that the boundaries between the two areas could be more blurred than commonly thought at the time. He wrote up his ideas on the matter in a book where topics connected to his stereochemical interests (*e.g.* asymmetry and life, enzymes) were dealt with.²¹ Furthermore, he presented a communication on the same subject at the “Congresso della Società per l’Avanzamento della Scienza”, Bologna, (from October 30 to November 5, 1926). The talk was scheduled for October 31 at the “Archiginnasio”, one of the most important buildings of the city. In the same day, the leader of fascism, Benito Mussolini, was visiting Bologna where the day before he had inaugurated the new stadium of the city (“Stadio del Littoriale”). Mussolini wanted to attend the meeting and to listen some lectures of special interest, including the talk of Betti.^{6,22} The meeting proceeded as expected. Mussolini gave a talk in which he urged chemists to do both fundamental and applied research. Furthermore, he was proud to mention the cases in which his government had spent a consistent amount of money to support scientific projects. The reader of this article will soon understand that this is the standard type of talk that even today any important politician would give at a scientific meeting. However, a difference does exist. Luckily enough, in Italy and in many other countries no politician would dare to share the opinion that Mussolini expressed by encouraging chemists to work in areas of interest for the needs of war-time.

At the end of his participation to the meeting, Mussolini left the building in a procession of cars. After a stretch of road, he was shot by a teenager, Anteo Zamboni (1911-1926). The Italian “Duce” remained uninjured, whereas the shooter was immediately captured and lynched by a crazy crowd. Lieutenant Carlo Alberto Pasolini was the first to identify and to catch Zamboni. The lieutenant was the father of Pier Paolo, (1922-1975), the famous Italian writer, poet, movie director and intellectual.²³

The comparison between man and mother nature in the matter transformation continued to be a fascinat-

ing topic for Betti. Meanwhile, his ideas were conveyed also to the man at the street. In some case the Betti's thoughts were not fully understood. In one article, the Italian newspaper “La Nazione” (April, 26-27, 1942) wrote: *At other times a man like professor Betti could undergo the risk of being sent to the stake.*⁶

A critical point was the fact that Betti oriented his interest not to philosophical problems concerning the reasons *why* things occur in nature but rather he wanted to know *how* they occur. In particular, due to his expertise, for Betti one of the most important questions was how the chirality problem might be brilliantly solved with one enantiomer selection in reactions involving asymmetric natural agents, whereas a chemist working with common reagents is inevitably bound to obtain only mixtures containing equivalent amounts of antipodal isomers. Indeed, several literature papers had shown the possibility of obtaining optically active material from a racemic mixture just by using the intervention of an enzyme as a catalyst that, due to its chemical nature, has many resolved stereo-centres. The process went through the preferential “destruction” of the faster reacting of the two isomers leaving unchanged and recoverable the slower reacting one.

Betti chose to evaluate a revolutionary innovation. The reaction of a normal Grignard reagent with aldehydes was performed to produce an alcohol, but instead of a common solvent he used optically active dimethylbornylamine. As a result, the alcohol showed a small but significant optical resolution, thus evidencing the first asymmetric synthesis based on the use of a chiral ligand.²⁴

We shall deal with this process in more details later on. For the moment, it seems more convenient to focus on the milestones of the route followed by Betti in his attempt to imitate mother nature. Indeed, almost at the same time, he wanted to check the possibility of using circularly polarized light as physical agent to induce asymmetry in the formation of an optical active compound. Attempts had been made by using racemic mixtures to effect an asymmetric destruction, reporting cases of success. Betti reasoned that chances could be higher by working in the gas phase, where intermolecular forces are weaker. For this reason, he chose to perform the reaction of addition of chlorine to propene. This process had also an additional advantage since it leads to a liquid product that separates from the gaseous reagents, in a way that, if a suitable reactor is used, the effect of the light after the addition reaction is avoided. This would makes unlikely any disturbing post-reaction on the liquid phase, such as an asymmetric destruction of the product. As a result of the actual experi-

ment, a weakly optically active 1,2-dichloropropane was obtained. The first asymmetric synthesis under the influence of circularly polarized light had occurred.^{25,26} However, as we shall see later on, this result was considered controversial.

During all his academic activity, Betti showed a great interest also on applied problems for which he used his capacity of innovation. Perhaps due to sentimental ties with his home town, he became a highly reputed expert of thermal water of many Italian regions. In this field he introduced the use of the mobile laboratory with which it was possible to analyse water at the spring. Another topic of interest was represented by chemistry and properties of rubber. The anti-gas mask used during world war one was significantly improved by him.⁶

Towards the end of the year 1941, the health problems of Betti became rather critical. Nevertheless, he continued to do research. A communication on the asymmetric synthesis was presented at a meeting of the Academy of Sciences of Bologna held on April 19, 1942. Mario Betti died on May 13. He was 67 years old.

On May 15, 1942 Bologna honoured the teacher and the scientist. The next day Bagni di Lucca honoured his son. More recently, the citizens placed a slab of marble on the external wall of the Betti's house that still include the antique pharmacy. The names of Mario and Adolfo Betti were engraved in the epigraph together with a few nice words recalling the merits of the two men.²⁷ Atoms and notes, reactions and scores, chemistry and music are now close together.

The life of Betti was spangled by a variety of honours and a full list would be to long. Just to mention a few, he was a member of *Accademia dei Lincei* and of the *Società Italiana delle Scienze detta dei XL*. In 1939, he was nominated Senator of the Kingdom of Italy. At that time the chairman of the Senate was Guglielmo Marconi, who had already received the degree of Doctor *Honoris Causa* in Physics from Betti, Dean of the Faculty of Sciences at the University of Bologna.

3. THE CHEMICAL HERITAGE OF MARIO BETTI

3.1 *The Transition Period*

Most of the top papers of the last period of the life of Betti had been co-authored by Elio Lucchi, who also worked at the same University. Unfortunately, due to an accident, he died a few months after the departure of the senior scientist. For this reason, the important work that was going on in Bologna suffered a stop. The passing of the torch had failed and the light on the Betti's chemistry became attenuated.

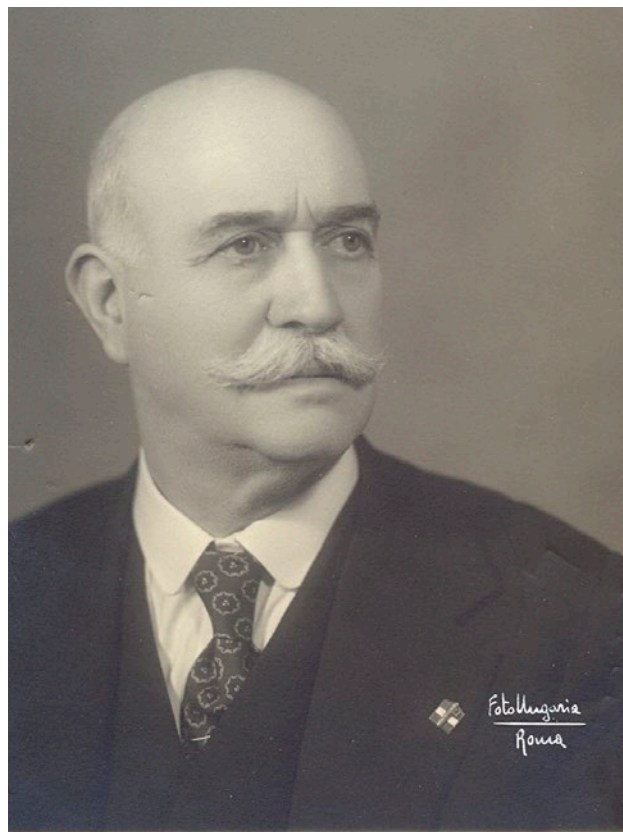


Figure 2. Mario Betti (Courtesy of dr. Massimo Betti).

During the same difficult period another great school of chemistry was rising in Bologna, *i.e.* the school of Industrial Chemistry. When Betti died, his former co-worker Bonino was the dean of the Faculty of Industrial Chemistry. In subsequent years he returned to the Ciamician Institute and the school of Industrial Chemistry was led by another farsighted great chemist, Angelo Mangini (1905-1988).²⁸ The building with the labs was located on a hill and the chemistry developed there was called “the chemistry of the hill” whereas the Ciamician Institute was downtown in the lowland. Under the leadership of Bonino and Mangini many difficulties deriving from the war times had to be overcome by both the “hill” and the “lowland” school. Eventually, within a reasonable numbers of years they were both able to reach a high standard and a great reputation.

In the years 1961-1968 Bertoluzza and Marinangeli of the Ciamician Institute published a series of papers²⁹ dealing with one of the Betti favourite themes, *i.e.* correlation between optical rotatory power and the nature of the group bound to the stereogenic centre. Betti had made extensive work and established a correlation between structure and optical parameter. Bonino, who

had co-authored several papers on the topic, considered the *Betti correlation* as “the most important contribution to organic chemistry of the earliest part of the 20th century”.⁸ The merit of Bertoluzza and Marinangeli was represented by the efforts of revisiting the correlation with a new approach that included theoretical calculations, u.v. spectroscopy, and circular dichroism. In my opinion, despite the interest stimulated by his correlation, nowadays the fame of Betti is supported by more solid bases and these will be dealt with in the following sections.

3.2. The Betti Reaction and the Betti Base

Thus far the attention of this article was focused on the “man Betti” and to the scenario where he played, whereas chemistry was only occasionally mentioned. Now, it is time to reverse the approach and to give a deeper insight into the activity of this great chemist, enlightening at least its most highest peaks.

As already said, in its original version the Betti reaction was represented by a multi-component process in which 2-naphthol, an ethanol solution of ammonia and 2 equivalents of benzaldehyde were involved. The product obtained in high yield could be described as deriving from the equilibrium between an imino- and an oxazino form. Treatment of the reaction mixture first with HCl and then with NaOH gave 1-(α -benzylamino)-2-naphthol. Many variations on the amino-reagent were considered, but it took a few decades to read about the possibility of replacing ammonia with a secondary amines. Indeed, in a work reported in 1935 by Littman and Brode,³⁰ dimethylamine and piperidine were successfully used.

Although commonly the research on this topic is focused on synthetic aspects, it seems reasonable that the reaction proceeds according to the following equations. The mechanism that was suggested as operating depended upon the nitrogen base used.

(i) Reaction with ammonia.

When ammonia is used, as in the case of the prototypical reaction, the first step of the reaction should be the formation of an imine (scheme 2), that would be then attacked by the carbon nucleophile at the 1- position of the naphthol (scheme 3):

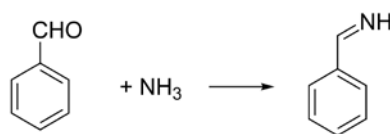
Once the Betti base **1** is formed, benzaldehyde easily leads to the imino-oxazino equilibrium between **2a** and **2b**, from which the final compound is regained by acid-base treatment (scheme 4).

A similar sequence would be followed when a primary amine is used.

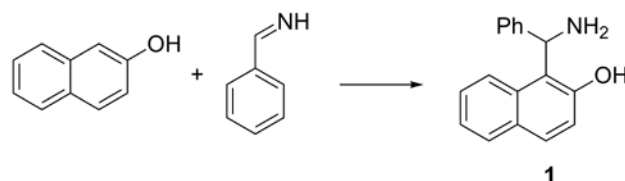
(ii) Reaction with secondary amines

For the reaction with a secondary amine, the production of an aminal **3** as intermediate was suggested by Littman and Brode (scheme 5).³⁰ The benzylidene diamine would then react with the carbon nucleophile leading to the final product by a substitution reaction.

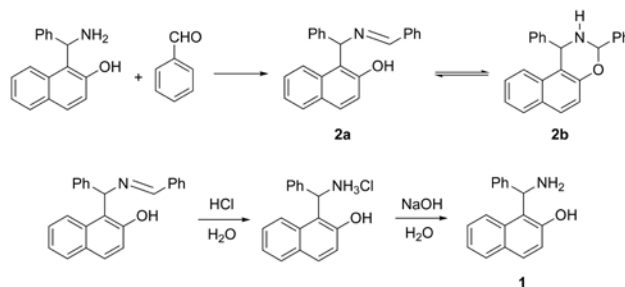
Often, the Betti reaction is referred to as a Mannich or a Mannich type reaction.³¹ Indeed, the two reactions are very similar both in a form and with substance. If instead of a naphthol we consider the enol deriving from a carbonyl compound suitable for the Mannich reaction we should envisage a behaviour very similar to the one reported above, provided that the oxazino-imino compounds are considered products deriving from the second attack of an aldehyde molecule. A problem arises when priority and name attribution to the two reactions are taken into account. Betti published his reaction in 1900,^{19a} whereas the paper of Mannich appeared twelve years later.³¹ Therefore, it is inappropriate to qualify the *Betti reaction* as a *Mannich reaction*. It would be tempting to do the reverse, but, after a century, it seems hopeless to modify a well established terminology practice. Tilting at windmills should be better



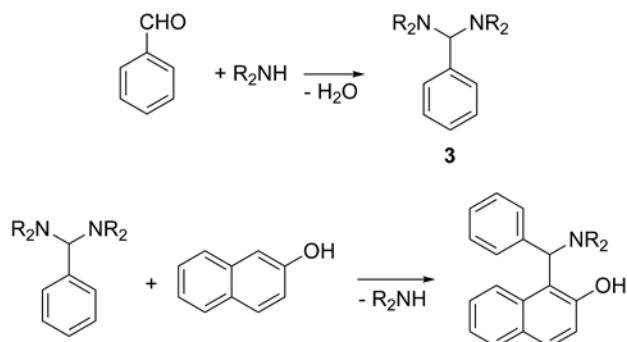
Scheme 2. Formation of the imine.



Scheme 3. Formation of the Betti base.



Scheme 4. Post-reaction and regeneration of the Betti base.



Scheme 5. Reaction with a secondary amine.

replaced with a factual recognition of the merit of the Italian scientist.

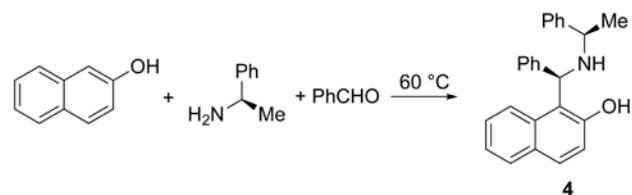
During his activity Betti was able to achieve a variety of optical resolutions and, actually, the first case that he studied was represented by his homonymous base, resolved with the classical procedure involving tartaric acid.²⁰ Since the possibility of obtaining a compound with high enantiomeric purity in a straightforward manner represents a convenient tool in organic synthesis, in 1998 at the University of Bari we undertook work concerning the preparation of the Betti base and similar structures, that we called using the plural form, *i.e.* Betti bases. Furthermore, we repeated the resolution of the prototypal base bringing minor changes to the original procedure and extending the resolution to other members of the family. The absolute configuration of 1-(α -benzylamino)-2-naphthol was established by X-ray experiments and this gave to us the possibility of assigning the configuration also to other bases.

Subsequently, prompted by our work, other research groups published important contributions reporting interesting and useful advances.⁵ A significant progress was achieved by Palmieri³² with the reaction between 2-naphthol, arylaldehydes and (*R*)-phenylethylamine in absence of a solvent (scheme 6). The product 4 resulting from the reaction with benzaldehyde was enriched up to of 99% in one optical isomer with two stereogenic centres.

3.3 Asymmetric Synthesis

The paper of Palmieri and co-workers leads us to the theme of stereodifferentiating reactions,³² that becomes of special importance when the scientific activity of Betti and his merits are presented.

In 1940 Betti e Lucchi reported that the reaction of benzaldehyde with methylmagnesium iodide in *N,N*-dimethylbornylamine as a solvent gave a 73% yield of



Scheme 6. Reaction between 2-naphthol, arylaldehydes and (*R*)-phenylethylamine.

1-phenylethanol showing an optical rotation of +0.30°.²⁴ The same alcohol was obtained with a rotation of +1.33° by reacting phenylmagnesium iodide with acetaldehyde in the same solvent.

In their work the two authors reported a scheme that clearly suggests the reason why the reaction could lead to optical active product, showing the interaction between ligand and metal in the nucleophilic attack. Such an interaction was fated to be the crucial aspect of a large number of reactions whose synthetic application have mushroomed under a variety of aspects.³³

Two years after the publication of Betti and Lucchi, their reactions were repeated by Tarbell and Paulson,³⁴ who were not able to reproduce the stereochemical results. These authors attributed the optical activity that Betti and Lucchi had found to the formation of an optical active impurity as by-product of the reaction. It would be tempting to compare carefully the details of the two papers reporting contrasting results and to search for the origin of the differences between the two couples of scientists. A detailed analysis was performed by Rosini³⁵ in an engaging paper characterised also by an elegant and enjoyable style. A possible source of the discrepancy could be attributed to a difference in the stereoisomeric composition of the amine used by the two groups, but the inadequate information available does not permit to reach a safe conclusion. Nevertheless, as appropriately commented by Noyori,³³ independently from the contrast existing between the results obtained in the two laboratories, the original concept of Betti and Lucchi remained valid. An undisputed proof appeared in 1953 when Cohen and Wright reported the reaction between ethyl benzoylformate and ethylmagnesium chloride in a mixture of benzene and (+)-dimethoxybutane.³⁶ The resulting ethyl 2-hydroxy-2-phenylbutanoate showed an extent of asymmetric synthesis reaching about 5%. Since the work of Cohen and Wright, the enantioselective alkylation of aldehydes was produced by many groups. A variety of ligands were used with enantiomeric excesses reaching very high values. The use of a catalyst having two co-ordinating centres, such as aminoalcohols, gave excellent results.

A large part of the merit that led Noyori to achieve the Nobel Prize in Chemistry 2001 derived from this type of synthesis.

In connection with our work concerning the exploitation of the Betti base, we entered the field with success by introducing ligands having the Betti base structural theme.^{4,5} After sixty years, the Betti original stereochemical idea was found to work at the best level by using the homonymous base. Rosini noted that the story presents some fascinating aspects.³⁵ As one would have expected, the work of our research group in Bari elicited (and is still eliciting) many other applications, thus enlarging the arsenal of chiro-methodologies available to the chemist.

3.4. Absolute Asymmetric Synthesis.

In the writing of Rosini a slight sensation of suspense accompanies the reader when the author deals with another paper by Betti and Lucchi concerning the synthesis of optically active substances.³⁵ The work was presented at the congress held in Italy in 1938, *i.e.* *X^o Congresso Internazionale di Chimica, Roma, Maggio 15-21, 1938*. The theme of the important meeting was rather appealing: *Chemistry at the service of human kind*. A detailed report of the work appeared in the second volume of the abstracts.²⁵ As usually, in the introduction Betti and Lucchi briefly review previous work made by others on the asymmetric synthesis performed in the presence of *dextro* or *levo*- circularly polarized light. In a few words, a different situation existed between asymmetric destruction of racemic compounds and asymmetric synthesis: experiments on deracemization had led to products showing optical rotation, whereas in the case of asymmetric synthesis no compound with a defined and stable optical activity had been obtained at the time. The experiment set up by the two Italian authors was represented by the gas phase addition of chlorine to propene to produce 1,2-dichloropropane. As already mentioned, a suitable apparatus was devised in order to separate the liquid product as soon as formed, thus avoiding an artefact connected with the possible deracemization of the produced chloroderivative. Eventually, in the experiment performed by Betti and Lucchi the dihalogeno-compound produced under the effect of *dextro* or *levo*- circularly polarized light was found to be optical active with rotations in the ranges from +0.040° to +0.050° and from -0.035° to -0.040°, respectively (the polarimeter sensibility was 0.005°). Three years after the Betti's death, Davis and Ackerman reported the absolute asymmetric synthesis of tartaric acid,³⁷ thus lending support to the feasibility of absolute

asymmetric synthesis. Surprisingly, three decades later Boldt and coworkers failed to carry out the asymmetric cyclopropanation reaction between diazoalkanes and trimethylethene under the effect of circularly polarised light.³⁸ The authors were then assailed with doubts concerning the possibility of achieving absolute asymmetric synthesis. Their doubts became even more consistent when they decided to repeat the chlorination of propene and the synthesis of tartaric acid. The results previously reported were not reproduced and the sad story was told in a paper in which the scepticism of the authors was made clear even in the title (*Sinde absolute asymmetrische Photosynthese möglich?*).³⁸ However, almost in the same period evidence against this excessive scepticism was obtained by the successful absolute asymmetric synthesis of epta- and octa-elicenes.³⁹ The reason of the difficulty met in the attempts to reproduce the Betti results remains unclear. The enigma appears even more surprising if one considers that in the case investigated by the Italian chemists it is not possible to invoke the formation of an adventitious by-product since the dichloropropane obtained in the reaction was characterised also by transformation into a different optically active compound, *i.e.* propylene glycol diacetate.²⁶ So no wonder that the mystery that wraps the process stimulates interest even nowadays.⁴⁰

Considering the discussion presented in both Sections 3.3 and 3.4, it seems wise to express the idea that the failure in reproducing results previously obtained by others cannot be taken as a verdict that the results are wrong. When discrepancies arise, extensive experiments should be repeated under strictly identical conditions. This is particularly valid when the expected results are associated to small values.

4. CONCLUSIONS

The end of the 20th century and the beginning of the present century have witnessed a steady increase in the production of work concerning the Betti chemistry, whose importance now is appreciated in its real dimensions. The present article has been written with the aim of reporting together with the life of Betti the peaks of his scientific and academic career. In spite of controversial aspects that inevitably occur in the activity of any great man, the stature of the chemist remains of a high standard. The trend of the impact of the work of the Italian scientist in chemistry reveals that this opinion is even bound to be enforced in the future. The high moral stature of the man revealed by his personal history represents an added value.

ACKNOWLEDGMENTS

I'm indebted to dr. Massimo Betti, the grandson of Mario, for kindly making available to me the couple of the manuscripts mentioned as ref. 6 and 7. It was a privilege for me to meet the ninth Betti generation of chemists and to have "first hand" information on the protagonist of this article. On the chemistry side, I wish to express my gratitude to my former co-workers drs. Cosimo Cardellicchio and Maria Annunziata Capozzi for sharing with me the enthusiasm to revisit the Betti chemistry world.

REFERENCES

1. P. Levi, *Lasimmetria e la Vita. Articoli e Saggi 1955-1987*, Einaudi Torino, **2002**, p.200.
2. P. Levi, L'inversione di Walden, *Tesi di Laurea in Chimica Pura*, Regia Università di Torino, **1941**.
3. C. Cardellicchio, G. Ciccarella, F. Naso, E. Schingaro, F. Scordari, *Tetrahedron: Asymmetry*, **1998**, *9*, 3667.
4. C. Cardellicchio, G. Ciccarella, F. Naso, F. Perna, P. Tortorella *Tetrahedron*, **1999**, *55*, 14685.
5. C. Cardellicchio, M.A.M. Capozzi, F. Naso, *Tetrahedron: Asymmetry*, **2010**, *21*, 507.
6. M. Betti, *Chi era Mario Betti*, Manuscript sent to the author by Massimo Betti on July 13, 2010.
7. M. Betti, *L'antica Farmacia Betti di Bagni di Lucca*, Manuscript sent to the author by Massimo Betti on July 13, 2010; see also <http://www.farmacibetti.it/storia.html>, last accessed 30/05/2017.
8. G. B. Bonino, *Discorso Commemorativo del Prof. Mario Betti Tenuto dal Prof. Giovanni Battista Bonino nell'Aula Magna dell'Università*, **1943**, Tipografia Compositori, Bologna.
9. S. Berlingozzi, *Gazz. Chim. Ital.* **1953**, *83*, 693.
10. A. Coppadoro, *Chimica e Ind.*, **1942**, *24*, 187.
11. www.arsc-audio.org/journals/v19/v19n1p25-62.pdf, last accessed 18/03/2017.
12. <http://pronetoviolins.blogspot.it/2014/06/adolfo-betti.html>, last accessed on, 18/03/2017.
13. M. Fontani, M.V. Orna, M. Costa, *Chimica e Chimici a Firenze. Dall'ultimo dei Medici al Padre del Centro Europeo di Risonanze Magnetiche*, Firenze University Press, Firenze, **2015**, 38.
14. M. Betti, R. Schiff, *Gazz. Chim. Ital.*, **1897**, *27*, II, 206.
15. M. Betti, R. Schiff, *Ber.* **1897**, *30*, 1337.
16. A list of 124 papers by Betti and coworkers is reported in ref. 9.
17. For a variation of the scale, see M. Fontani, M. Costa, *Chimica e Ind.*, **2011**, *93*, 106.
18. For reviews of the work on the topic, see M. Betti, *Gazz. Chim. Ital.*, **1923**, *53*, 417; M. Betti, G. B. Bonino, *Memorie Accad. Sci. Istituto Bologna*, **1925-1926**, [8], *3*, 39; **1929-1930**, [8], *7*, 81; *Trans Far. Soc.* **1930**, *26*, 337.
19. (a) M. Betti, *Gazz. Chim. Ital.*, **1900**, *30*, II, 310; (b) *Organic Syntheses*, **1929**, *9*, 60.
20. M. Betti, *Gazz. Chim. Ital.*, **1906**, *36*, II, 392.
21. M. Betti, *Problemi e Aspetti della Chimica della Materia Vivente*, **1926**, Zanichelli, Bologna.
22. A. Charachalios, *Giovanni Battista Bonino and the Making of Quantum Chemistry in Italy in the 1930*, in: *Chemical Sciences in the 20th Century. Bridging Boundaries*, C. Reinardt ed., Chap. 4, p.75, Wiley VCH, Weinheim, **2008**.
23. <https://storiadimenticate.wordpress.com/2012/10/31/anteo-zamboni/>, last accessed on 31/05/2017.
24. M. Betti, E. Lucchi, *Boll. Sci. Fac. Chim. Ind. Bologna*, **1940**, I-II, 2.
25. M. Betti, E. Lucchi, *Ricerca Sci.*, **1937**, *8*, II, 130; *Atti X Congresso Int. Chimica*, Roma, **1938**, *2*, 112.
26. M. Betti, E. Lucchi, *Memorie Accad. Sci. Ist. Bologna*, **1942**, *IX*, 203.
27. <http://www.chieracostui.com/costui/docs/search/schedaoltre.asp?ID=11081> , last accessed on 01/04/2017.
28. F. P. de Ceglia (Ed.) *Scienziati di Puglia, Secoli V a.C.-XXI d.C.: Angelo Mangini e i Misteri della Chimica Organica dello Zolfo*, Adda Editore, Bari, **2007**, p. 551.
29. A. Bertoluzza, A.M. Marinangeli, *Annali Chim.* **1961**, *51*, 322; **1961**, *51*, 981; **1962**, *52*, 731; **1964**, *54*, 1020; **1968**, *58*, 205.
30. J. B. Littman, W. H. Brode, *J. Am. Chem. Soc.*, **1935**, *52*, 1655.
31. C. Mannich, W. Krosche, *Arch. Pharm.*, **1912**, *250*, 1647.
32. C. Cimarelli, A. Mozzanti, G. Palmieri, E. Volpini, *J. Org. Chem.* **2001**, *66*, 4759.
33. R. Noyori, M. Kitamura, *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 49.
34. D. S. Tarbell, M. C. Paulson, *J. Am. Chem. Soc.*, **1942**, *64*, 2842.
35. G. Rosini, *Rendiconti Accademia Nazionale delle Scienze Detta dei XL. Memorie di Scienze Fisiche e Naturali*, **2003**, *27*, 1.
36. H. L. Cohen, G. F. Wright, *J. Org. Chem.*, **1953**, *18*, 432.
37. T. L. Davies, J. Ackerman, Jr., *J. Am. Chem. Soc.*, **1945**, *67*, 486.
38. P. Boldt, W. Thielecke, H. Luthe, *Chem. Ber.*, **1971**, *104*, 353.

39. W. J. Bernstein, M. Calvin, O. Buchardt, *J. Am. Chem. Soc.* **1972**, 94, 414; **1973**, 95, 527; *Tetrahedron Letters*, **1972**, 2195; H. Kagan, A. Moradpour, J. F. Nicoud, G. Balavoin, R. M. Balavoine, R.H. Martin, J. P. Cosyn, *ibid.*, **1971**, 2479. See also, A. Guijarro, M. Yus, *The Origin of Chirality in the Molecules of Life*, RCS Publishing, Cambridge, **2009**, p. 48.
40. <https://ilblogdellasci.wordpress.com/2017/05/22/qualcuno-puo-aiutarmi-a-spiegare-un>, last accessed on 25/05/2017.