Willstätter Memorial Lecture.

RICHARD WILLSTÄTTER.

DELIVERED AT THE CHEMICAL SOCIETY, BURLINGTON HOUSE, ON NOVEMBER 6TH, 1952.

By SIR ROBERT ROBINSON, O.M., F.R.S.

RICHARD WILLSTÄTTER died at Muralto-Locarno in Switzerland on August 3rd, 1942, barely a week before he would have attained the span of three-score years and ten. The joys and sorrows of his life reached the greatest heights and depths of human feeling and we can never be too grateful for his autobiography " Aus meinem Leben," completed in 1940 but published posthumously in 1949, which gives such a clear picture of his happiness and exaltation, as well of his grievous disappointments and tragic losses. The wealth of material contained in this moving narrative, as well as the volume and variety of his contributions to the scientific literature, doom to failure any attempt to describe his life and work completely. It is only possible to glance superficially at some of the outstanding achievements and perhaps to give a summary which will assist in the reading of his own somewhat discursive account, in which philosophic reflections on the tasks and duties of the teacher and investigator, as well as on many other matters, are interspersed among the biographical and the scientific topics.

There have lived highly distinguished organic chemists who have filled the literature with important work over a long period of years and have nevertheless contributed little more than developments predictable on grounds of analogy. A small select band were recognisably pioneers, even great pioneers. Such were Liebig, Baeyer, and Emil Fischer, and assuredly such a one was Willstätter. He broke entirely fresh ground both as the result of the attack on the most difficult objectives and also in the devising of new methods for the solution of these problems. Hardly anything he started was finished and the measure of his success and brilliance is the extent of the territory which he opened up and failed to explore. The true pioneer—bahnbrechend—can never reach the end of the journey. Naturally the earlier stages represented the gain of solid ground, but the man who is enabled to push ahead by these conquests more often than not reaches the most fertile country. In illustration of this we may refer to Hans Fischer's work on chlorophyll or to the post-Willstätter developments of enzyme chemistry. In neither case is it suggested that Willstätter was the only pioneer on whose work the later developments were based, but he was one of them.

Willstätter has told us that his panacea and corrective for the effects of all the vacillations of fortune was " work " and then " more work."

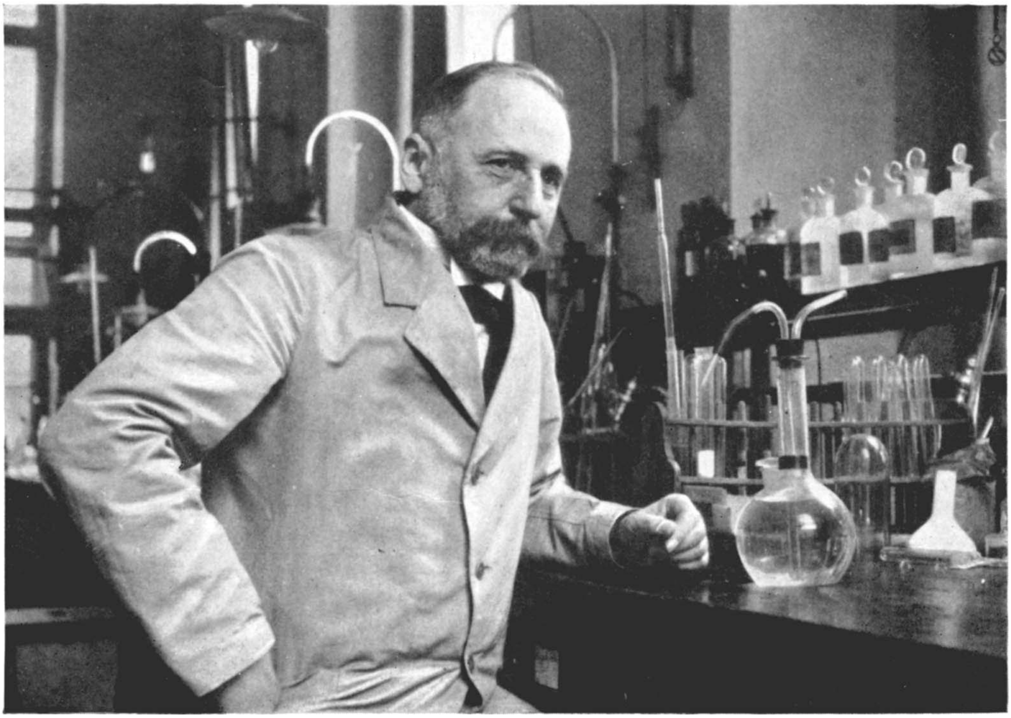
I turn at once to some of the fields in which he laboured. In doing this it will be necessary to jump over considerable gaps in the years and hence a brief statement of the framework of his academic career will give points of reference.

At the age of 18 he entered the University of Munich where he became in a general sense a pupil of Baeyer, though he never worked in collaboration with that great master. In due course he became Privatdozent and then Professor extraordinarius. In 1905 he accepted the Chair of Chemistry at the Zürich Polytechnic, and in 1912 was called as Director of the Kaiser Wilhelm Gesellschaft Institut at Dahlem, Berlin. He followed Baeyer at Munich in 1915—16 and resigned in 1925, continuing however to direct a cell of research in the laboratory.

In 1939 he was fortunate to be able to leave Munich and he lived at Muralto-Locarno from that time until the end.

Tropine, Cocaine, and Hyoscine.—When the young student in February, 1893, was ready to embark on research with a view to a Doctorate he was most anxious to work under Baeyer but he did not suggest this and was assigned to Professor Alfred Einhorn who acted as his supervisor. Einhorn did good work in several fields and especially on cocaine and synthetic local anæsthetics; he had no official position in the laboratory and occupied a tiny room for thirty years. Willstätter records with approval the regular attention and careful guidance he gave to his collaborators. Unfortunately, Willstätter's eventual success in this group of alkaloids of solanaceous plants was displeasing to Einhorn, as well as to Ladenburg, who evinced bitter hostility.

Einhorn and Tahara treated the methiodide of anhydroecgonine ethyl ester with silver oxide and obtained an amino-acid, $C_{10}H_{15}O_2N$, which evolved dimethylamine when boiled with aqueous sodium hydroxide, affording an acid, $C_8H_8O_2$, isomeric with toluic acid. When this



Richard Willstätter.

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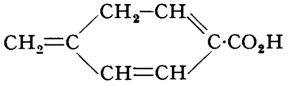
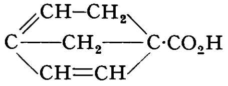
was heated with hydrobromic acid a dihydrobromide was produced and the latter gave *p*-toluic acid with hot aqueous alkali. Quite naturally the substance was regarded as dihydro-*p*-methylenebenzoic acid (I). Willstätter was invited to make a further study of this reaction and his first paper,* with Einhorn (*Ber.*, 1893, **26**, 2009), describes the tetrahydro-derivative of the acid, which was still unsaturated to permanganate, and its conversion into an isomeride under the influence of hot aqueous sodium hydroxide.

(I)





(II)

The outcome of further studies described in a long paper in *Annalen* (1894, **280**, 96—159) was the formula (II), of which the methylene bridge was broken so as to yield *p*-toluic acid derivatives and also the *cyclo*hexane ring with assumed production of ethyl*cyclo*pentane derivatives. Bredt's rule had not yet been formulated! Arising from this interest Willstätter also studied the reduction of aromatic acids by means of sodium and amyl alcohol, a technique which he emphasises was invented by Baeyer. Salicylic and *m*-hydroxybenzoic acids were converted into hexahydro-derivatives, but in later experiments the former acid was converted into pimelic acid by ring-scission at the keto-acid stage. A correction was published (*Ber.*, 1894, **27**, 331), but Willstätter considered (cf. " Aus meinem Leben," p. 445) that the hexahydro-acid had actually been obtained in the first experiments and claimed good agreement with the properties of the acid later synthesised by W. Dieckmann (*Ber.*, 1894, **27**, 2475) in the Munich laboratory.

A thesis on the above topics was presented and, after an examination which he was told would be a matter of form but in which he was nevertheless asked to recite the entire Periodic System horizontally, he received the Doctorate " *summa cum laude* " a mark which Willstätter doubted he had deserved and which he thought must have been decided in advance.

This was at the end of his seventh semester in 1894; in June of the previous year he read his first paper on hydrogenated *p*-toluic acids before the Munich Chemical Society. His performance was praised by Baeyer—" you spoke like an experienced Professor "—who thereafter kept in frequent touch with one whom he doubtless already recognised as a budding genius. The laboratory in which Willstätter worked was shared with Petrenko-Kritschenko and others, but the Director paid more attention to Willstätter than to one of his own co-workers named Bihan who was also in this room, and assisted him both with his thesis and with the preparation of the paper in the *Annalen* to which reference has already been made.

After the early Doctorate the question arose as to what career he should seek to follow. Einhorn, who had suffered a reverse at Aachen, advised against an academic career, and proposed a post in industry. Considering the cocaine problem finished he decided to abandon it himself and after some discussion forbade Willstätter any further work in this field. But doubts persisted and it seemed absolutely necessary to resolve them. Hence Willstätter sought a way out and devoted attention to tropine instead of cocaine. This was certainly rather naïve and Professor Einhorn broke off all relations and did not resume them so long as Willstätter remained in Munich.

However, Baeyer himself approved the plans which were gradually taking shape and at this critical period gave great help and encouragement to the young Doctor. Independent work began in 1894, and in 1896 Willstätter became Privatdozent. He had been held back for two years by Merling's presence in the laboratory in Thiele's organic chemistry section. This prohibited the projected work on tropine which was justly regarded as Merling's prerogative. Now Merling went away to industry and the way lay open ahead. Willstätter made arrangements with the firm of E. Merck in Darmstadt and thus obtained an assured supply of material at a reasonable price. This arrangement was later developed into a consultancy and was doubtless found advantageous by Merck.

Merling had oxidised tropine, $C_8H_{15}ON$, to tropinic acid, $C_8H_{13}O_4N$, and recognised that $\cdot CH_2\cdot CH(OH)\cdot$ had become $2CO_2H$. He had replaced the Ladenburg formula (III) by a superior expression (IV) which yielded tropinic acid (V). Willstätter therefore determined to degrade tropinic acid, and the clue was given by a test-tube experiment in which it was observed that the methiodide of tropinic ester gave a basic ether-soluble oil when warmed with potassium carbonate solution. He had opened the ring and the rest should be easy. He was entranced, fascinated, and stood back to admire, to wonder at his good fortune and to plan. In fact it

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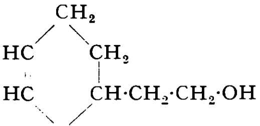
* In " Aus meinem Leben " this honour is given to a paper on the separation of cocaine from other alkaloids (*Ber.*, 1894, **27**, 1523).

appears to the Lecturer that he took an unconscionably long time before he decided that the fruits were ripe enough to gather.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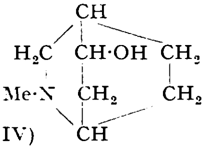
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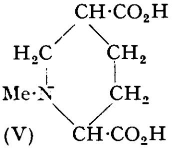
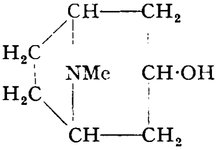

(V)

He went on a holiday and visited his mother at St. Anton am Arlberg. There in the Post Hotel the idea occurred to him to oxidise tropine to the ketone tropinone and to take advantage of its reactivity to lay bare further secrets of the tropine molecule. There followed a great deal of wrestling with the spirit in order to determine how best to proceed. However, he now realised that he had two keys, a magic one and a systematic one, and his whole world was transformed. He went to the United States to visit relations and during a week of sea-sickness the oil from the methiodide was a comforting picture in the mind. The methiodide was indeed described as the talisman which protected the " Salier," a small Australian ship, from sinking in violent storms—the journey occupied fourteen days, and the ship sank on its next voyage. I have dwelt on this because Willstätter himself made it clear that he regarded this experiment as the turning point of his scientific life.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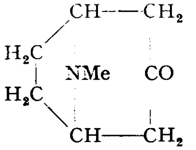
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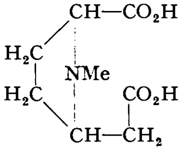
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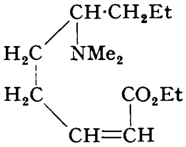
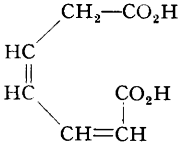

(IX)

On return from America the Hofmann degradation was pursued but it was not until several years had passed that the degradation to pimelic acid was finally completed. This proved the presence of seven carbon atoms in a straight chain in tropinic acid and a seven-membered ring in tropine. Before the culmination of this work the latter was indicated by the other method. Careful oxidation of tropine with chromic acid gave a beautiful basic ketone, namely tropinone, and this afforded a dibenzylidene derivative and thus contained $\cdot CH_2\cdot CO\cdot CH_2\cdot$. Merling's formula for tropine was therefore modified to (VI) in 1898 and the eventual degradation to pimelic acid (XI) was realised through tropinone (VII), tropinic acid (VIII), the des-base (IX) from ethyl tropinate methiodide, and the second Hofmann stage (X), reduced to (XI) by means of sodium amalgam.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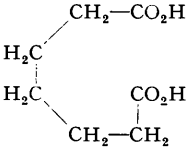
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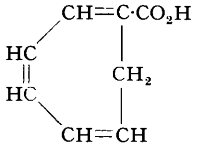
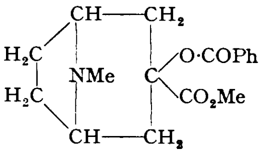

(XII)

The first part of the work on tropinone was published at once on the advice of Baeyer, and this was just as well since, independently, G. Ciamician and P. Silber of Bologna made similar progress.

It became clear, four years after the *Doctor-arbeit*, that dihydro-*p*-methylenebenzoic acid was *cyclo*heptatrienecarboxylic acid (XII). On reduction with sodium and alcohol, tropinone gave, not tropine, but *pseudo*tropine, and *pseudo*tropine could be re-oxidised to tropinone. This was important in two directions. First, it demonstrated the relation of tropine to *pseudo*-tropine and laid the foundation for later stereochemical studies. But, secondly, it made *pseudo*tropine readily accessible and from this the valuable tropacocaine could be prepared. Thus was industry rewarded for its help to academic research.

Furthermore, Willstätter had the curiosity to prepare an isomeride (XIII) of cocaine by way of tropinone cyanohydrin. Merling, who was then a director of Schering and did not share the bitterness of Ladenburg or the coolness of Einhorn, visited the Munich laboratory and saw a specimen of (XIII) on Willstätter's table. He took the hint and applied the same idea to piperidones more readily accessible than tropinone with the result that the eucaines were developed. α-Eucaine (XIV) was the close analogue of Willstätter's substance but this proved too irritating, and β-eucaine (XV), which is built on the tropacocaine (benzoyl*pseudo*tropine) model, replaced it and was manufactured on a large scale. Baeyer objected to what he regarded as the picking of the brains of University men but Willstätter thought it a natural and desirable collaboration.



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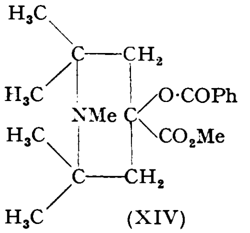

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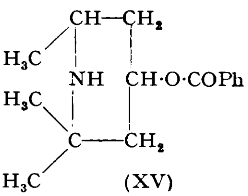


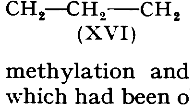
(XV)

In the summer of 1896 Willstätter wrote his habilitation thesis on " Investigations in the Tropine Group." In November of that year he lectured on his chosen theme and defended it attired in tails and white kid gloves. Incidentally he overturned the blackboard.

After this ordeal it seems that he became more involved in teaching duties and had less time for research. The tempo certainly slowed down a little but he soon resumed full activity and was determined to effect the synthesis of atropine and of cocaine. As already indicated, the discovery of dibenzylidenetropinone and the constitution of tropine belong to 1897 and 1898 respectively. In the latter connexion certain improbable alternatives were found to be inconsistent with the facts. Among the more important of these were the formation of 2 : 3-dihydrobenzaldehyde by the action of alkalis on tropinone methiodide and the oxidation of tropilene (a *cyclo*heptadienone) to adipic acid.

In 1898 (*Ber.*, **31**, 2498) he showed that tropilidenecarboxylic acid (XII) gave *cyclo*heptanecarboxylic acid on reduction with sodium and amyl alcohol This acid had already been synthesised by Spiegel, but Willstätter nevertheless degraded the acid from cocaine into suberone by brominating it, replacing the bromine by hydroxyl, and oxidising the hydroxy-acid with lead peroxide, a sequence of operations often used by Baeyer. At the same time he recognised that tropilidene was *cyclo*heptatriene and hydrotropilidene was *cyclo*heptadiene.

These hydrocarbons obtained as end-products of the Hofmann degradation series of tropabases were the chosen starting points for a most elegant synthesis by retracing the steps. The successful execution of this daring design has always impressed the Lecturer as a very great achievement. It is set aside in our text-books, or rather in some of them, and was even deprecated by Willstätter himself because of its complexity and the poor yield, and because a quicker method was later found to be feasible But it traverses a very rich field of chemistry and has the special interest which always attaches to a synthesis which reverses a step-wise degradation. A much simpler example of the same kind is furnished by Claisen's synthesis of chelidonic acid, which incidentally was much improved by Willstätter in an important practical detail, namely, substitution of potassium ethoxide for sodium ethoxide in the preparation of acetonedioxalic ester. This work culminated in 1901 and 1902 in the syntheses of tropilidene and tropidine and the conversion of tropidine into tropine. Suberone was the source of suberylamine and *cyclo*heptene, the dibromide of which afforded (XVI) with dimethylamine. Further



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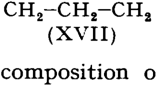

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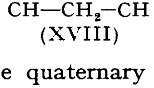

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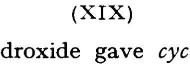

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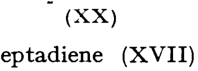
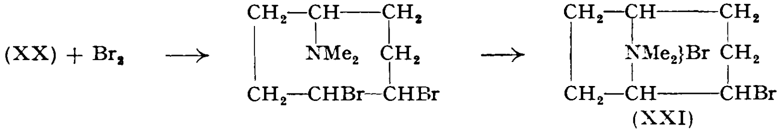


(XX)

methylation and decomposition of the quaternary hydroxide gave *cyclo*heptadiene (XVII) which had been obtained by Hofmann degradation of dihydrotropidine. The two hydrocarbons were identical. The dibromide of (XVII) yielded tropilidene (*cyclo*heptatriene) (XVIII) on being heated with quinoline. Now came the retracing of the steps. The hydrobromide of tropilidene reacted with dimethylamine to form α-methyltropidine (XIX) which is obtained from tropine by dehydration to tropidine, methylation of this base, and des-base formation by pyrolysis of the quaternary hydroxide. The reconversion of methyltropidine into tropidine had been effected by Merling, but Willstätter could not reproduce the process to his satisfaction and employed instead the dihydromethyltropidine (XX) which can be prepared by reduction of methyltropidine with sodium and alcohol. (XX) was brominated in hydrobromic acid solution and when the base was liberated and taken up in ether it underwent trans-annular ring-closure to bromodihydrotropidine methobromide (XXI). The bromo-methobromide (XXI) readily lost the elements of hydrobromic acid with warm alkali, and the resulting tropidine methobromide was converted into the iodide and thence into the chloride, and the latter furnished tropidine (XXII) when heated. Addition of hydrogen bromide to the double bond of tropidine proceeds in the desired direction and hydrolysis [$\cdot CHBr \cdot \longrightarrow \cdot CH(OH) \cdot$] could be effected by dilute sulphuric acid at 210°. This gave *pseudo*tropine and hence tropinone. Earlier the reduction of tropinone to tropine had been effected by zinc and hydriodic acid, or by cathodic reduction in acid solution.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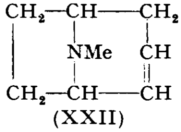
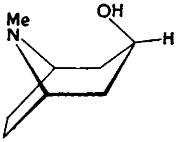

(XXII)

Thus was the synthesis of atropine and other tropines completed and the only structural problem that remained was the question of the configuration of tropine and *pseudo*tropine.

At least one well known text-book erroneously attributes this isomerism to a *cis-trans*-relation between the Me in NMe and the hydroxyl group. It is rather a question of the whole NMe group (or the ethylene bridge) in *syn-* or *anti*-relation to the hydroxyl. Only this year the problem has been solved by Professor G. Fodor who finds that *pseudo*tropine (XXIII) has a *syn-* and tropine (XXIV) an *anti*-configuration.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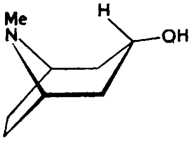

(XXIV)

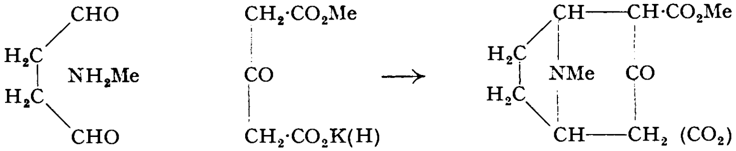
The much more complex stereochemistry of the ecgonines has also been cleared up so far as the two better-known isomerides are concerned. Work on the synthesis of natural cocaine spread over a long period of years.

On the analogy of the preparation of camphorcarboxylic acid, the carboxylation of sodiotropinone was attempted and found to succeed. In 1901 in collaboration with Bode the reduction of the sodium tropinonecarboxylate with sodium amalgam was found to yield chiefly *pseudo*tropinecarboxylic acid and a by-product in small amount which was thought to be γ-ecgonine and this was converted into a γ-cocaine. Twenty years later it was pointed out by Willstätter and Bommer that the γ-cocaine of 1901 was not $(\pm)$-cocaine but $(\pm)$-ψ-cocaine. In 1923 by collaboration with O. Wolfes and H. Mäder of the Merck laboratories it was possible to work on a much larger scale and the reduction of methyl tropinonecarboxylate afforded $(\pm)$-ψ-ecgonine methyl ester and also a little $(\pm)$-ecgonine methyl ester. The latter was converted into $(\pm)$-cocaine and the racemate resolved as the hydrogen $(+)$-tartrate and hydrogen $(-)$-tartrate. $(\pm)$-ψ-Cocaine was found to be an excellent local anæsthetic, said to be free from habit-forming properties; it was placed on the market under the name " psicaine."

However, we must go back to 1917 for the beginning of these later phases : In that war year the Lecturer published an account of a simple synthesis of tropinone from Harries' succindialdehyde, methylamine, and calcium acetonedicarboxylate. There had been a gap of many years in the appearance of Willstätter's papers and the experiment had some bearing on a possible shortage of atropine, which was needed in the field.

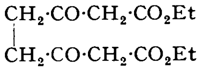
Although it might have been regarded as an intrusion, how different was the reaction of Willstätter from that he himself experienced in early days from older colleagues ! When it became possible to do so, he wrote the Lecturer a charming letter expressing his pleasure and at a later meeting the only thing that troubled him was the use of dipiperonylidenetropinone for identification purposes; the dibenzylidene derivative was, he said, a sufficiently beautiful substance. The explanation that a new derivative was made by a young chemist as a matter of principle appeared to satisfy him.

The flattery received was partly that which is said to bear the hall-mark of sincerity. Careful hydrolysis of methyl acetonedicarboxylate afforded a dipotassium compound which was a semi-ester. This was condensed with succindialdehyde and methylamine to give methyl tropinonecarboxylate (XXV). This was the method developed in 1923 for the synthesis of psicaine.

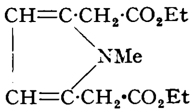

(XXV)

The dipotassium monoethyl ester had been earlier used in an ingenious manner for another simple synthesis made at Dahlem (with Pfannenstiel, 1921): by Kolbe–Walker electrolysis it yielded diethyl 2 : 5-diketohexane-1 : 6-dicarboxylate (XXVI) which with methylamine gave ethyl 1-methylpyrrole-2 : 5-diacetate (XXVII). Catalytic hydrogenation of this gave the corresponding pyrrolidine derivative and an application of the Dieckmann reaction converted this into ethyl tropinonecarboxylate. The pyrrolidine derivative (XXVII + 4H) has also been made by Karrer and Alagil (1947) from crotonic acid by ω-bromination, coupling with silver, addition of hydrogen bromide to two double bonds, and treatment of the product with methylamine.

(XXVI)

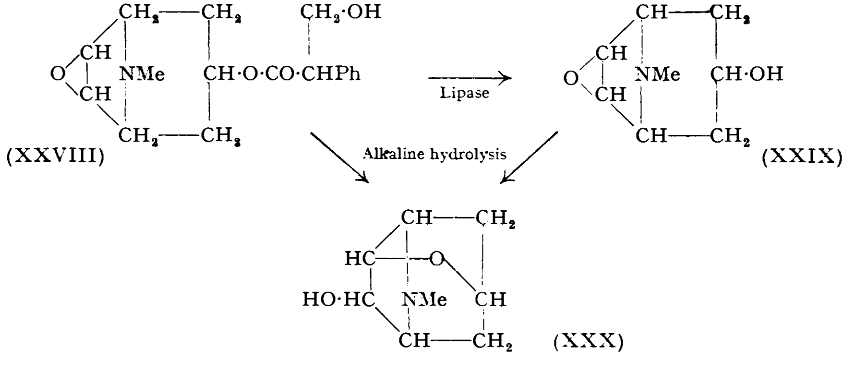


$$\begin{array}{l} CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et \\ | \\ CH_2{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et \end{array}$$


(XXVII)

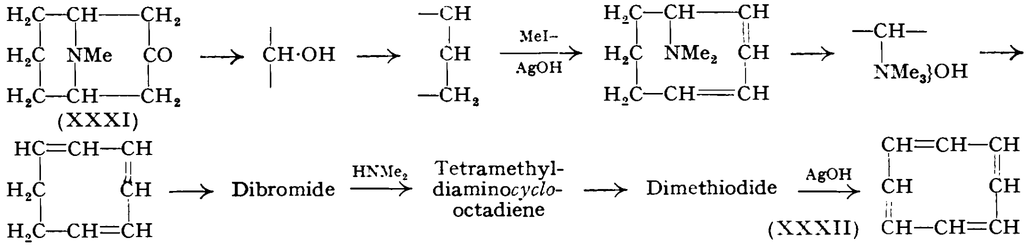
In 1907 Willstätter and Heubner investigated a base $C_8H_{20}N_2$ found by Merck in *Hyoscyamus muticus*. It was proved to be 1 : 4-bisdimethylaminobutane, $NMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$. This finding is one of the pillars of the Lecturer's theory relating the solanaceous alkaloids to ornithine. 1-Methylpyrrolidine and other simple bases have been found in the solanaceae but they have not all been fully examined.

Willstätter and Berner made an important contribution to the chemistry of hyoscine (or scopolamine) which they hydrolysed by pancreatic lipase to tropic acid and scopine (XXIX), and thus avoided the isomeric change into oscine (XXX) which occurs very easily in presence of alkalis. Along with the earlier work of Hesse, Luboldt, Hess, Schmidt, and Willstätter and Lessing, who in 1902 synthesised a degradation product, namely 1-methylpiperidine-2 : 6-dicarboxylic acid, this result gave strong confirmation to the constitution (XXVIII) proposed by H. King for hyoscine.



The early work on lupinine was carried out by Willstätter in 1902 in collaboration with Fourneau, one of the most distinguished of his pupils. They established the main features of the chemistry of the alkaloid and recognised the existence of a bicyclic nucleus The full constitution was developed by Karrer and confirmed by syntheses due to Clemo and Winterfeld and their respective co-workers.

The alkaloids of pomegranate bark are ring-homologous with the solanaceous bases and have been investigated by, *inter alios*, Tanret, Hess, Meisenheimer, Wibaut, and especially Piccinini. Piccinini's formula (XXXI) for *pseudo*pelletierine was advanced by analogy with tropinone. Willstätter degraded the base in several ways and obtained *cyclo*octadiene, *cyclo*octatriene, and finally *cyclo*octatetraene (XXXII). The methods closely followed those which he had worked out in the *cyclo*heptane series. This work of Willstätter and Waser (1910 and 1911) was confirmed with Heidelberger (1913). It excited very great interest because of the non-benzenoid character of the hydrocarbon. A large amount of scepticism as to the nature of the hydrocarbon was expressed by American chemists, some of whom went so far as to suggest that the hydrocarbon was styrene. These criticisms were made on various grounds of a theoretical nature and did not include a repetition of Willstätter's experiments until Cope and Overberger (1947 and 1948) undertook this and confirmed the complete accuracy of the work.

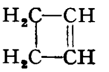

(XXXI) (XXXII)

The brilliant researches of Reppe during the second World War showed that acetylene can be polymerised in the presence of nickel cyanide with formation of *cyclo*octatetraene and other hydrocarbons. Large quantities thus became available and the confirmation of Willstätter's work is remarkably close. This is shown in the following Table (compiled by Dyson).

Properties of cyclo*Octatetraene.*

	Reppe	Willstätter
B. p./760 mm.	142—143°	—
B. p./17 mm.	42·0—42·5°	42·2—42·4°
M. p.	$-7°$	$-27°$
d_4^0	0·9382	0·943
d_4^{20}	0·9206	0·925
n_D^{20}	1·5290	1·5389
Mol. refraction	35·17	35·2
Mol. exaltation	$-0·09$	$-0·12$

Much earlier (in 1905) Willstätter and von Schmaedel prepared the gaseous *cyclo*butene (XXXIII) by the decomposition of *cyclo*butyltrimethylammonium hydroxide but they were unable to remove two hydrogen atoms so as to obtain the lower vinylogue of benzene. The methods employed were too robust.


(XXXIII)

The separate existence of *cyclo*butene and butadiene (as well as of the pair dihydrobenzene and hexatriene) is a proof that stable electromers are possible, for both substances contain the chain CH_2·CH·CH·CH_2 and differ only in the distribution of valency electrons. It is very satisfactory that Willstätter made the experiments because there can be no doubt about the correctness of his record. Indeed Zelinsky hazarded the suggestion that *cyclo*butene was bicyclic but Willstätter and Bruce (1908) gave reasons for rejection of this possibility.

Reduction and Oxidation.—One of the greatest claims that Willstätter makes on our gratitude is in connexion with the new experimental methods which he introduced, examples of which abound in our sequel. He was fond of simple reactions—oxidation, reduction, and hydrolysis—and sharpened our tools for all these operations. How often in the work at which we have already glanced would the process of catalytic hydrogenation not have proved a boon ? Although he did not discover the value of noble metals in promoting hydrogenation at the ordinary temperature (observed by Fokin in 1907), he was the first to apply the method systematically; he greatly improved the technique and showed, for example, the importance of the presence of oxygen in the catalyst. He prepared in this way dihydrogeraniol, dihydrophytol, dihydrocholesterol, hexahydrobenzoic acid, *cyclo*hexane, decahydronaphthalene, pyrrolidine, and many other compounds, and observed the inhibiting influence of impurities, especially of sulphur (Willstätter and Meyer, 1908; Willstätter and Hatt, 1912). In 1913 Willstätter and King prepared pure dihydronaphthalene from tetrahydro-β-naphthylamine and hydrogenated it easily to tetrahydronaphthalene which was further hydrogenated very slowly. But naphthalene itself always afforded decahydronaphthalene directly on hydrogenation, so that the reaction stages must be different, or perhaps we have another instance of the reactivity of nascent molecules.

In the hydrogenation of phthalic anhydride and naphthalic anhydride the presence of oxygen was found to be essential (Willstätter and Jaquet, 1918). Stranger still, the acids themselves are hydrogenated in absence of oxygen (or with less oxygen) but the anhydride, present even in traces, stops the process, which may be carried forward if oxygen is introduced. The experiments referred to ordinary platinum black on the one hand, or the metal loaded with oxygen on the other.

In 1921, with Waldschmidt-Leitz, the matter was probed more deeply. It was shown that platinum free from oxygen is not a hydrogenation catalyst at all and that the same circumstances apply to nickel. Recognition of this led to the adoption of the device of reactivation by shaking with air.

Typical of his scrupulous attention to detail is a considerably later study of reduction by sodium amalgam (Willstätter, Bumm, and Seitz, 1928). The influence of impurities in the amalgam was stressed and it was found that pure sodium amalgam is a powerful and rapid reducing agent with a very high utilisation of the available hydrogen. The theory was formulated that the amalgam is not active through the formation of nascent hydrogen but rather by addition of sodium to the ethylenic group in the first phase of the reaction. This amounts to very much the same idea as the prevailing conception of reduction by sodium in ammonia (cf. A. J. Birch).

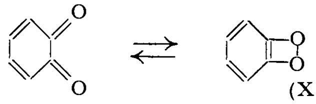
Willstätter also studied oxidation catalysis and found (with Sonnenfeld, 1913) that metallic osmium, especially in the colloidal condition, facilitated the oxidation of unsaturated substances by oxygen at the ordinary temperature. *cyclo*Hexene was converted into 2-hydroxy*cyclo*hexanone and other substances. Later, conditions were found for oxidizing ethylene to glycol. No use appears to have been made of the method which, however, was the forerunner of other processes. Willstätter (with Bommer, 1921) even studied the oxidation of ethylene to formaldehyde by aerial oxygen at 595° and showed that a 50% yield was obtainable. Curious results were obtained in a study of the joint action of phosphorus and oxygen on unsaturated compounds (with Sonnenfeld, 1915). The elements of P_2O_3 or P_2O_4 could be introduced and the products were called phosphorites or phosphorates respectively. For example, *cyclo*hexene phosphorate was a pale yellow crystalline powder, $C_6H_{10}O_4P_2$, which could be oxidised by nitric acid with formation of *cyclo*hexenephosphonous acid, $C_6H_9{\cdot}PO_2H_2$.

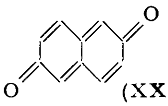
Researches on Quinones and Quinone Imines.—A long series of papers that appeared between 1905 and 1912 was concerned with the preparation and properties of quinonoid substances.

In 1905 Willstätter and Pfannenstiel obtained the hitherto unknown *o*-benzoquinone by oxidation of catechol in ethereal solution with silver oxide. The dark red transparent plates were odourless, non-volatile, and easily reducible to catechol. Three years later (with Müller) a colourless modification was obtained by carrying out the oxidation for only fifteen seconds at a low temperature. It was easily transformed into the red modification and was apparently in equilibrium with it since both forms separated when an ethereal solution of the red form was strongly cooled. The red variety was assumed to be the usual dicarbonyl compound, and the colourless a benzenoid peroxide (XXXIV).

In 1907 the new method was applied to 2 : 6-dihydroxynaphthalene and a third *amphi*-naphthaquinone (XXXV) was obtained. This substance forms reddish-yellow prisms, has a normal molecular weight in benzene, and is reducible to the dihydric phenol. A similar dichloro-derivative was also prepared and found to be much more stable.

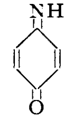
Willstätter's collaborator in this work was J. Parnas who later became Professor of Physiological Chemistry at the University of Lemberg. The usual oxidising agents, namely, silver oxide and lead peroxide (often in presence of anhydrous sodium sulphate or magnesium sulphate), were employed, but it was also decided to try gold oxide. The substance exploded on being touched with a spatula and fragments of gold entered the eye. All but the smaller ones could be removed and Parnas' sight was not permanently impaired.

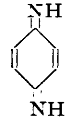

(XXXIV)


(XXXV)

Willstätter, Mayer, and Pfannenstiel (1904) prepared two further simple prototypes in *p*-benzoquinone monoimine (XXXVI) and di-imine (XXXVII). They could be obtained by oxidation of *p*-aminophenol or *p*-phenylenediamine, respectively, with silver oxide in ethereal solution in the presence of sodium sulphate Their properties were unexpected since both substances were found to be colourless. The monoimine exploded spontaneously when dried; it reacted at once with alkaline phenol to give an indophenol, and with dimethylaniline in acid solution to give phenol-blue. The di-imine was more stable but showed similar reactions. Corresponding *N*-methylimines were also obtained and these had similar characteristics. Many other significant results were obtained in the course of this work—the preparation of diphenoquinone in red and colourless modifications (benzidine, however, gave diaminoazodiphenyl, $NH_2 \cdot C_6H_4 \cdot C_6H_4 \cdot N_2 \cdot C_6H_4 \cdot C_6H_4 \cdot NH_2$) and of quinone azine, $O{:}C_6H_4{:}N \cdot N{:}C_6H_4{:}O$, from *p*-azophenol, may be mentioned.

(XXXVI)





(XXXVII)

A similarly constituted bright red quinone could be obtained from *p*-dihydroxystilbene but this had already been prepared by Zincke and Fries in a different manner.

Willstätter paid much attention to the Würster dye-salts and to quinhydrones and propounded theories to explain their properties. These are perhaps of doubtful significance at the present time but plenty of facts were recorded for the use of anyone who now wishes to collate the material on modern lines (cf. Sidgwick's "Organic Chemistry of Nitrogen," Baker and Taylor, Oxford Univ. Press, 1937, pp. 99—101). It should also be mentioned that the scope of Willstätter's method of oxidation in an anhydrous solvent was not confined to phenols and amines. It was found that arylhydroxylamines could be easily oxidised in this way to corresponding nitroso-compounds (1908).

A problem to which Willstätter made a definite, but perhaps not a final, contribution was that of "aniline black." This was of interest to him in connexion with the problem of the course of the oxidation of aniline to *p*-benzoquinone. The idea had been advanced that the stages were phenylhydroxylamine, *p*-aminophenol, and quinoneimine, but this was rejected since the conversion of phenylhydroxylamine into *p*-aminophenol does not occur under the conditions of the oxidation process.

A green salt was obtained by Nover (1907) by electrolytic reduction of nitrobenzene; this gave a blue, crystalline base $(C_6H_5N)_x$ termed "emeraldine." The formation of this substance goes back to Nietzki who oxidized *p*-aminodiphenylamine with ferric chloride (1879) and probably obtained "emeraldine."

Willstätter and Moore (1907) obtained the base termed "azurine," as deep blue, microscopic prisms, m. p. about 165°, and found that it was $C_{24}H_{20}N_4$. On oxidation with lead peroxide in benzene it afforded $C_{24}H_{18}N_4$, red leaflets which polymerised in water at 150—170° to a black mass. This substance, $C_{24}H_{20}N_4$, was regarded as $Ph \cdot NH \cdot C_6H_4 \cdot NH \cdot C_6H_4 \cdot N{:}C_2H_4{:}NH$. Evidence was soon forthcoming that this chain was doubled and oxidised in the various "aniline blacks."

Willstätter and Dorogi (1909) oxidised aniline with one quarter of the amount of chromic acid necessary for the formation of quinone and obtained after careful purification what they considered to be pure "aniline black." The substance was shown to be $C_{48}H_{36}N_8$ and this gave a quantitative yield of quinone on oxidation with lead peroxide and sulphuric acid, but only 85% of the theoretical amount with chromic acid. The explanation was provided by the behaviour of $O{:}C_6H_4{:}NPh$ which gave quinone from both nuclei when treated with lead peroxide and sulphuric acid but only from one nucleus (maximum, 50% yield) when chromic acid was employed. The quantitative yield of quinone obtained from the supposed "aniline black" showed that all the links are *para* to nitrogen, and the oxygen consumed in its formation showed that the C_{48} molecule was three times quinonoid. These conclusions were later confirmed by Green using Knecht's titanous salt titration method.

The formula proposed (XXXVIII) accounts also for the 85% of quinone obtained by chromic acid oxidation. The nucleus between the dotted lines can also become quinonoid, two

$$NPh{:}C_6H_4{:}N \cdot C_6H_4 \cdot \vdots NH \cdot C_6H_4 \cdot NH \cdot \vdots C_6H_4 \cdot N{:}C_6H_4{:}N \cdot C_6H_4 \cdot N{:}C_6H_4{:}NH \qquad \text{(XXXVIII)}$$

hydrogen atoms being removed by means of hydrogen peroxide. The triquinonoid substance is now termed nigraniline, and the tetraquinonoid, pernigraniline. Both afford exactly one-eighth of their nitrogen as ammonia on hydrolysis. Moreover the hydrolysed product from pernigraniline with one CO terminally situated is dead black and is not "greened" by sulphur dioxide, as are other members of the series.

All this is very clear and convincing and evidently a major contribution to the subject but the view that one of Willstätter's nigranilines, partly hydrolysed or not, was identical with the "aniline black" produced on the fibre by dyers was contested in the same year by Bucherer. He preferred an azine constitution for the commercial dyestuff in order to explain its high degree of stability. Green and Woodhead (1910) agreed that Willstätter had thrown much light on the earlier stages of "aniline black" formation and concurred in the conception of the linking of eight aniline molecules in a chain. But they claimed that some of Willstätter and Dorogi's products were mixtures and regarded nigraniline as an intermediate product in the formation of "aniline black."

The short controversy that followed was painful to Willstätter and perhaps we may summarise the outcome by suggesting that Willstätter's results apply to the reactions carried out under the laboratory conditions in solution, whereas "aniline black" produced on the fibre with other reagents and under quite special conditions may very well be something different. Willstätter and Cramer (1910) confirmed the earlier work with Dorogi by study of the reduction of the substances in various stages of oxidation with phenylhydrazine carbamate over a range of temperature. In the course of a strong reply (1911) to Green and Woodhead they state that titanous chloride only reduces nigraniline to the monoquinoid stage, but that the true leuco-compound can be obtained by treatment with phenylhydrazine at 150°. This, it was claimed, was a source of error in Green and Woodhead's findings. We cannot presume to adjudicate, but it is at least fair to point out that the Willstätter picture is on the canvas, whereas the azine conception exists, so far as the Lecturer is aware, only in the artist's mind.

Chemistry of Chlorophyll.—The ambition to solve the most difficult problems presented by the chief plant pigments was formed in early days and was confided to Baeyer who gave every possible encouragement. It is hard to realise now how very little was known about these colouring matters or to estimate the courage and confidence that inspired the young enthusiast. The work began in Munich but the translation to Zürich in 1905 provided a fuller opportunity, and the first paper on chlorophyll, jointly with W. Mieg, appeared in 1906. Among the more important precedents of Willstätter's work were the researches of Stokes (1864) who not only showed spectroscopically that the chlorophyll of green leaves is a mixture, but employed partition between alcohol and carbon disulphide to separate the components.

Schunck (1885, 1888) and Marchlewski studied the regulated action of alkalis and acids on crude chlorophyll and obtained a number of mixed degradation products and at least one nearly homogeneous "phylloporphyrin" which gave a sparingly soluble zinc salt. J. Borodin (1882, 1884) observed "crystalline chlorophyll" which separated from alcoholic extracts and is now known to be ethyl chlorophyllide. There was also a considerable parallel development of the chemistry of the blood pigment (Hoppe Seyler, Nencki and Zaleski, Piloty, Küster, and others). Chemists in quite early days sensed intuitively the close relation existing between chlorophyll and the blood pigment, perhaps first expressed by Verdeil in 1851, but it was left to Willstätter and Hans Fischer to place this theory on a firm basis of ascertained fact.

Like his predecessors, Willstätter at first worked with extracts, and these were made from dried leaves of the stinging nettle, which were extracted with light petroleum in order to remove carotenoids and then exhausted by hot or cold alcohol, or ethyl acetate. A series of phytochlorins and phytorhodins was obtained from these extracts by the action of acids and alkalis and separated by taking advantage of different basic strengths. Immediately following this paper is one by Willstätter alone in which he criticises Stoklasa's lecithin-type theory of the nature of chlorophyll, because he had already obtained chlorophyll preparations which were free from phosphorus. One of the methods was based on that of Sorby (1873) and developed by Kraus. Willstätter used methyl alcohol and light petroleum as the partly miscible solvents instead of ethyl alcohol and benzene. The ash was 1·84%, nearly all magnesium oxide. In this memoir the hydrolysis of chlorophyll to chlorophyllin, a substance of acid character containing magnesium (3·54% as MgO), and an alcohol, later called phytol, approximately $C_{20}H_{40}$, were described.

In the following year (with Hocheder, 1907) it was roundly stated that chlorophyll is a complex magnesium compound and the magnesium was shown to be removed by oxalic acid in alcoholic solution. The magnesium-free pigment was termed phæophytin. The composition of phytol was confirmed. At this stage some doubt was expressed regarding the identity of chlorophyll from different plants and some divergence was noted in the product of hydrolysis of phæophytin from grass and that from algæ. This was later traced by Willstätter and Stoll (1910) to differences in phytol content due to the action of an enzyme, chlorophyllase, which occurs in all the green parts of plants. Examination of a very large number of species (>200) showed that the chlorophyll was substantially identical in all of them.

The degradation series was continuously enlarged in a long series of memoirs. The dicarboxylic acid obtained by mild hydrolysis with alkalis was termed chlorophyllin. It contained magnesium which was not lost when it was heated with alcoholic potash on the water-bath, yielding blue glaucophyllin, and then at 200° yielding rhodophyllin (with Pfannenstiel, 1907).

These results were amplified and extended by Willstätter and Fritzsche in 1910 with a wealth of descriptive detail of the various derivatives. The chlorophylls were recognised as derived from a tricarboxylic acid and to contain the common nucleus $C_{31}H_{34}N_4Mg$. Rhodophyllin is a dicarboxylic acid and was used for the final degradation to an oxygen-free porphyrin. With alcoholic potash at 250° a monocarboxylic acid can be obtained but, after that, decomposition of the molecule occurs. Hence rhodophyllin in small quantities at a time was strongly heated with soda-lime and afforded ætiophyllin, $C_{31}H_{34}N_4Mg$, from which ætioporphyrin, $C_{31}H_{36}N_4$, could be obtained by the action of acids. The reconversion into ætiophyllin was effected by means of ethereal methylmagnesium iodide (Willstätter and M. Fischer, 1913). The abbreviated table below illustrating the degradations does not take later work into account. The work of Borodin (1882) on crystalline chlorophyll was developed by Monteverde (1893) and confirmed by Willstätter and Benz (1908). It was then noted that crystalline chlorophyll did not contain phytol, and the erroneous suggestion was made that one of Stokes' two chlorophylls might be free from phytol. The truth was reached stepwise. At first, crystalline chlorophyll was thought to contain two methoxy-groups, that is $2CO_2Me$, but in collaboration with Stoll (1910) it was established that the crystalline material is the result of ethanolysis and contains one CO_2Me and one CO_2Et. Chlorophyllase is an esterase and can not only hydrolyse the original phytyl ester but also synthesise a carbethoxy-group from the same carboxyl group. A little later the same authors effected a partial synthesis of chlorophyll from chlorophyllide and phytol. At about the same time closer attention was paid to the proof of the identity of chlorophyll in different plants, and also to the isolation of pure chlorophyll and the separation of the two components of chlorophyll. For all this work the crystalline ethylchlorophyllide provided a valuable standard for colorimetric comparison.

In one investigation (with Hug, 1911) the dried leaves were made into a meal, extracted with benzene and then light petroleum, and then with about 1·5 l. of alcohol per kg. of meal in 2—3 hours. The alcoholic solution was shaken with light petroleum and water, and the chlorophyll purity reached 33—40% in the light petroleum; washing with aqueous methanol (90%) raised this to 50—60%, and on further washing with 95% methanol (saturated with light petroleum) the purity became 70%. In this last process half the chlorophyll was dissolved in the methanol. The alcoholic solution was washed with light petroleum, and this final solution was washed with water with the addition of sodium sulphate whereupon the chlorophyll was precipitated. It was purified by dissolution in alcohol and precipitation with brine, followed by dissolution in ether and precipitation with light petroleum. 0·75 G. was obtained from 2 kg. of dried nettle leaves containing about 15 g. of chlorophyll.

This chlorophyll corresponded to $C_{55}H_{72}O_6N_4Mg$. It was a mixture of two components chlorophyll-*a* and chlorophyll-*b*. These were separated (with Isler and Hug, 1912) by a tedious process of distribution between light petroleum and methanol, whereby chlorophyll-*a* accumulated in the hydrocarbon layer and chlorophyll-*b* in the methanolic phase.

Chlorophyll-*a* was finally isolated as a bluish-black microcrystalline powder,

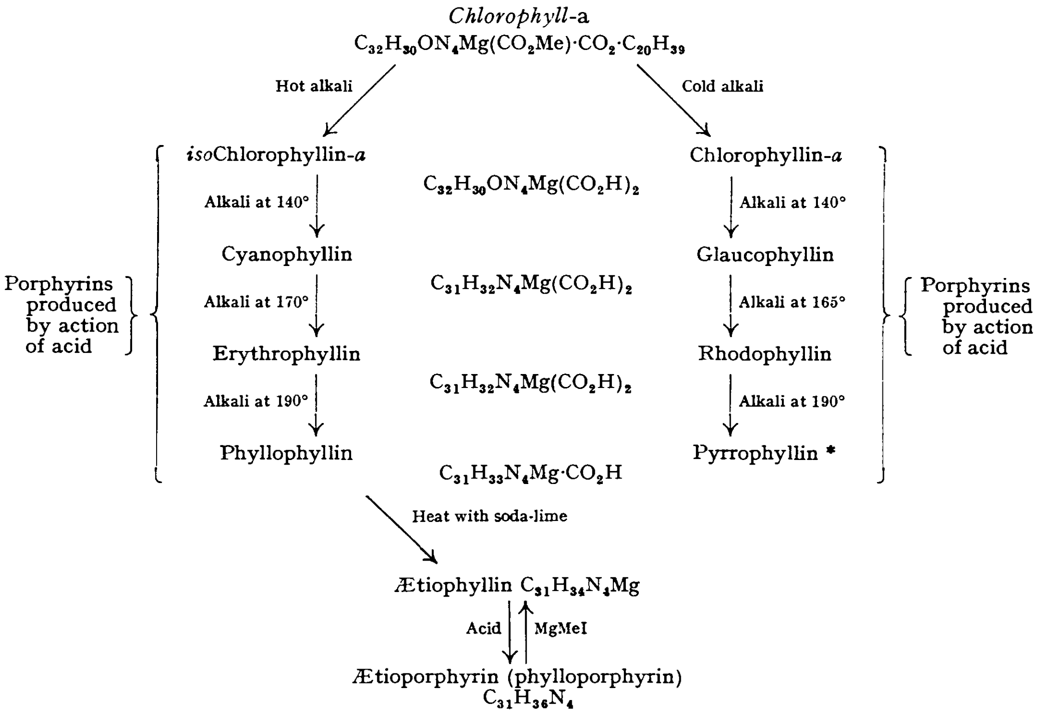
$$C_{32}H_{30}ON_4Mg(CO_2Me)\cdot CO_2\cdot C_{20}H_{39},0{\cdot}5H_2O,$$

and chlorophyll-*b* as a greenish-black, microcrystalline powder, $C_{32}H_{28}O_2N_4Mg(CO_2Me)\cdot CO_2\cdot C_{20}H_{39}$. These formulæ have stood the test of time and their establishment in such a short period of years represented a new level of achievement in the technique of organic chemistry. Nothing of this kind had been previously accomplished. It is true that Stokes had proved the coexistence of two chlorophylls and that Tswett separated them chromatographically on columns of sugar or calcium carbonate, but there is as much difference between those investigations and Willstätter's as there would be between the identification of a new element with the mass spectrometer and its isolation in substance from a mineral. The difference between chlorophyll-*a* and chlorophyll-*b* is that 2H in the former are replaced by O in the latter. It is now known that -Me in -*a* is -CHO in -*b*. The absorption spectra of -*a* and -*b* are largely complementary and together cover a great range of wave-lengths in the visible region. This suggested that the mixture is by no means an accident but is required for more efficient use of sunlight in photosynthesis.

A similar table could be constructed to illustrate the derivatives of chlorophyll-*b*.

The more complete degradation of chlorophyll derivatives was studied with Asahina (1910, 1912) by oxidation and reduction.

Phylloporphyrin, pyrroporphyrin, rhodoporphyrin, and phytochlorin were oxidised by chromic acid or in other ways, and it was found that 1 mol. of any of them afforded 1 mol. of hæmatic acid and 2 mols. of ethylmethylmaleinimide. Since according to Küster, and also Piloty, hæmin yields about 2 mols. of hæmatic acid and no ethylmethylmaleinimide under similar conditions, it followed that at most two, and possibly only one, of the pyrrole nuclei in the two series are similarly substituted.



* It is now known that phyllophyllin is a methyl pyrrophyllin. The degradation of pyrrophyllin yields eventually pyrroætioporphyrin, $C_{30}H_{34}N_4$. This substance and also phylloporphyrin have been synthesised by H. Fischer, finally demonstrating the close relation of the plant and animal respiratory pigments.

It was already known in a general way that vigorous reduction of chlorophyll gave rise to chlorophyll-pyrrole which was evidently similar in character to the alkylpyrroles obtained from the blood pigment. Malarski and Marchlewski (1910), moreover, claimed to have identified chlorophyll-pyrrole with hæmopyrrole by preparation of the phenylazo-derivatives. The details submitted were not, however, quite sufficient for the purpose.

Willstätter and Asahina repeated the reduction of hæmin by means of hydriodic acid and phosphonium iodide (Nencki and Zaleski) and of hæmatoporphyrin following Piloty, and then applied both methods to various chlorophyll derivatives of which phylloporphyrin was found to be the most suitable. Three homologous pyrroles were isolated, and phyllopyrrole and hæmopyrrole (then called *iso*hæmopyrrole) were proved to be identical from all sources, but there was at first a difficulty about cryptopyrrole (then called hæmopyrrole) which was soon resolved by H. Fischer and Bartholomäus.

In 1913 Willstätter and M. Fischer attempted a still closer correlation of the leaf and blood pigments. On the incorrect working hypothesis that the difference between the porphyrins from the two sources was probably a question of orientation of the carboxyl groups, it was obviously desirable to equate the two series by removing the carboxyl groups. This was carried out and the investigation added much to our knowledge of hæmin derivatives. The ætioporphyrin from hæmin was found to be identical with that from chlorophyll despite minor differences. The composition with C_{31} was still maintained. However, later work by H. Fischer showed that Willstätter's ætioporphyrin was a mixture of homologues and that pure ætioporphyrin is $C_{32}H_{38}N_4$.

The difficulties of analysis and identification need not be emphasised. It was only the complete synthetic survey that enabled H. Fischer to reduce this group to order in later years, and we may recall that he also stumbled once in this territory when he identified the first synthetic ætioporphyrin-I with the natural product.

Willstätter was unable to accept the Küster formula for the porphyrins because of the assumed improbability of the sixteen-membered ring and he proposed a tetrapyrrylethane structure on which it is unnecessary to dwell. This involved awkward manœuvres to include two more carbon atoms. H. Fischer attempted to harmonise the Küster and the Willstätter representation but in the sequel his amazing industry and brilliance not only led to the firm establishment of the Küster porphin ring but also to the synthesis of hæmin and probably to the full elucidation of the constitution of the chlorophylls-*a* and -*b*. With these later developments we are not concerned and that they have a pioneering character we shall not deny, but will only claim that Willstätter cleared a part of the way, and that where the obstacles could only be removed by a giant.

It was realised that, apart from the two ester groups, a carboxyl group was latent in chlorophyll; Willstätter thought it likely that the substance was a lactam. We now know that the third carboxyl is set free by hydrolysis of a β-keto-ester group.

The study of the chemistry of phytol was begun by Willstätter, who at one stage suggested that it might be related to isoprene.

It was not until 1928 that F. G. Fischer finally showed that it is indeed a member of the diterpenoid group possessing the constitution :

$$Me_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CMe{=}CH{\cdot}CH_2{\cdot}OH.$$

In 1913 Willstätter and Stoll published a book entitled " Untersuchungen über Chlorophyll," and a Lecture on this subject delivered to the Deutsche Chemische Gesellschaft on April 25th, 1914, will be found in *Ber.*, 1914, **47**, 2831.

*Carbon assimilation in the green leaf.** The researches (1915—18) of Willstätter and Stoll on the rôle of chlorophyll in carbon assimilation were a natural sequel of the discovery of the nature of the pigment and especially of its content of magnesium. The suspicion could hardly be avoided that iron in hæmoglobin, and magnesium in the plant chromo-protein, have analogous but complementary functions. It was found that photosynthesis could not be effected by isolated chlorophyll and that the rate of assimilation was not proportional to the chlorophyll content. A co-operating enzymic process was postulated and it was thought that this might be concerned with the decomposition of a chlorophyll–carbon dioxide compound with liberation of oxygen.

They found that chlorophyll was not the limiting factor in the process but also that abundant chlorophyll facilitated an increase of photosynthesis with rise of temperature.

We know far less of the chlorophyll–protein complex than we do of hæmoglobin. It is certainly a loose and variable combination and all the results already mentioned and many others of similar character appear to be explicable if it is the chromo-protein as a whole which is responsible for carbon assimilation. The analogy of hæmoglobin supports this view. By using an apparatus in which carbon dioxide was passed over leaves contained in an illuminated glass vessel and with every condition in control, it was found that the quotient, CO_2 absorbed/O_2 evolved, was strictly unity at various temperatures, and at various concentrations of oxygen or carbon dioxide, and with leaves from several kinds of plants.

This was held to support the view, first propounded by Baeyer in 1870, that formaldehyde is the first product of photosynthesis. The quotient for formaldehyde is 1, whereas it is 1·33 for glycollic acid, 2 for formic acid, and 4 for oxalic acid. The statement has been made that glycollic aldehyde is the only other compound that can give the ratio unity. There is, however, an unlimited number of such compounds. All we need is $nCO_2 + xH_2O \longrightarrow C_nH_{2x}O_x + nO_2$. The quotient is therefore unity for all carbohydrates and substances like acetic acid, lactic acid, orsellinic acid, phloroglucinol, etc., which have the same state of oxidation as a carbohydrate.

In 1917 Willstätter and Stoll found that carbon dioxide decomposed chlorophyll in colloidal solution with formation of magnesium hydrogen carbonate and phæophytin. Evidence was obtained, however, that an intermediate product was formed in which the chromophoric group, magnesium, and carbon dioxide were bound together.

It was also found possible to regenerate chlorophyll and carbon dioxide from this intermediate. The conclusion that a similar process operates in the leaf would appear to be irre-

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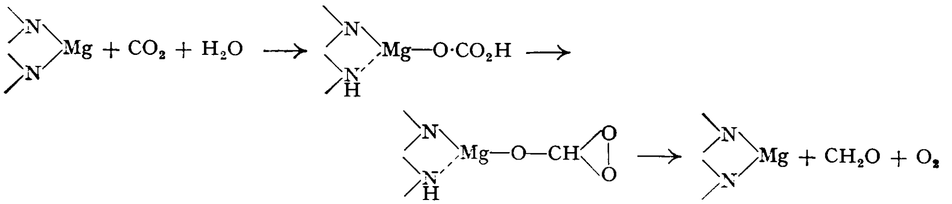
* A complete account is contained in Willstätter and Stoll's " Untersuchungen über die Assimilation der Kohlensaüre," Springer, Berlin, 1918.

sistible, but differences in the circumstances were noted. Once again a chromo-protein must be evoked to help us to understand the contrast in behaviour of chlorophyll *in vitro* and *in vivo*.

The hypothesis was advanced that the photosynthetic process in the leaf is an action of light on the compound of carbon dioxide and chlorophyll, whereby a peroxide is produced capable of parting with oxygen in the gaseous form. The transformation below was considered feasible.



Carotenoids.—The preliminary extraction of stinging nettle leaves with light petroleum gave a yellow solution and the pigments responsible for the colour were separated and examined. Similar substances had been previously described but Willstätter may be said to have initiated the modern phase of the study of the carotenoids, so ably carried further by two of his pupils, Kuhn and Zechmeister, as well as by Karrer, Heilbron, and others.

In 1907 Willstätter and Mieg showed that leaf carotene is identical with the already known substance from carrots and they found by analysis and molecular-weight determination that the formula is $C_{40}H_{56}$, and not $C_{26}H_{38}$ as suggested by Arnaud many years earlier. Many interesting new properties of carotene were recorded, including its autoxidation and the formation of a dark violet, crystalline iodide.

A second substance separated from carotene by partition between partly immiscible solvents was termed xanthophyll, $C_{40}H_{56}O_2$, which also formed a violet iodide and on aerial oxidation gave a microcrystalline substance $C_{40}H_{56}O_{18}$. Later (with Escher, 1910) carotene and xanthophyll were each shown to yield derivatives with 22 atoms of bromine, but it is doubtful whether the compositions of these substances were accurately ascertained. Willstätter's carotene, m. p. 170°, was later shown to be a mixture of isomerides. He was the first to notice that an odour of violet roots developed on exposure of carotene to oxygen.

Lycopene, the colouring matter of the tomato, had been studied by Millardet, Schunck (who established its separate identity), and Monteverde. Willstätter and Escher showed that it is isomeric with carotene, more sensitive to oxygen, and reacting with bromine to give $C_{40}H_{44}Br_{26}$. The di-iodide was formed as a dark green precipitate.

In 1912 the same authors proposed a division of the pigments of these types into two groups, namely, the pigments soluble in light petroleum and those more readily soluble in the simple alcohols. Carotene and lycopene belong to the former type, and xanthophyll to the latter.

A new representative of the xanthophyll group was discovered in lutein, the colouring matter of the yolk of eggs. Lutein was found to be isomeric with xanthophyll and to have a similar absorption spectrum. Several of its properties and derivatives were described.

Many other workers had studied xanthophyll or preparations containing xanthophyll but it was not until Kuhn, Winterstein, and Lederer (1931) examined xanthophyll from various sources by means of chromatographic analysis that the true position was made clear. Xanthophyll from all these sources was separated into two distinct compounds of which the more abundant was called " lutein " in agreement with Willstätter. The term xanthophyll is more generic. Willstätter and Stoll (1918) were unable to detect any influence of the carotenoids on the process of photosynthesis. In autumnal fading the carotene diminishes but the xanthophyll appears to increase in relative amount.

Willstätter did not discover the carotenoids or determine the constitution of any one of them. He was content to make a fundamental contribution that greatly facilitated the work that followed so very quickly and has resulted in the writing of a fascinating chapter of Organic Chemistry.

The Red, Purple, and Blue Colouring Matters of Flowers, Fruits, and Leaves.—The isolation of the anthocyanins and the study of their chemistry are among the finest of Willstätter's achievements and display his genius in a very clear light. It is necessary to recall that the instability and variety of the flower pigments were not attractive to those in search of easy conquests and it is curious that not even any of the dyestuff chemists, familiar with the properties of basic dyes such as the azines, had the least inkling of the nature of these substances. The Lecturer remembers that the late V. J. Harding in 1907 asked for his views on the subject. Without any consideration the reply was that they were probably azo-dyes because nothing else could have the range of shade.

The only difficulty was in overcoming the initial resistance and once the chemical type was located, the whole field lay open. To the conqueror of chlorophyll it was something like a chemical massacre. Excellent accounts of the subject are to be found in texts such as Perkin and Everest's " The Natural Organic Colouring Matters," Longmans Green, 1918, or Mayer and Cook's " The Chemistry of Natural Colouring Matters," Reinhold Publ. Corp., A.C.S. Monographth No. 89, 1943.

The first observations on the colour of flowers were made by Robert Boyle in 1664 who wrote in his " Experiments and Considerations touching Colours " : " Take good Syrrup of Violets, Impraegnated with the Tincture of the flowers, drop a little of it upon a White Paper . . . and in this Liquor let fall two or three drops of Spirit of Salt or Vinegar, or almost any other eminently Acid Liquor and upon the Mixture of these you shall find the syrrup immediately turned Red. . . . But to improve the Experiment let me add what has not . . . been hitherto observed . . . namely that of instead of Spirit of Salt . . . you drop upon the Syrrup of Violets a little Oyl of Tarter *per Deliquium* or the like quantity of Solution of Potashes and rub them together, you shall find the Blue Colour of the Syrrup turned in a moment into a perfect green." This green colour is produced from a yellow due to a flavonol and from a blue due to an anthocyanin. The indicator character of anthocyanins was also noted by Nehemiah Grew (1682). After that we have to wait for Berzelius who in 1837 attempted the isolation of certain of the pigments and used the method of precipitation of lead salts and regeneration with hydrogen sulphide. The work did not lead to the preparation of any pure substance but this process was later used by Willstätter in certain cases. Morot (1850) attempted the preparation of the cornflower colouring matter by precipitation of its aqueous solution with alcohol, the first stage in the method later developed by Willstätter and Everest. Glenard (1858), Heise, and also Glan (1889—94) attempted the separation of pigments from the various sources by Berzelius' method or a slight modification thereof (use of ethereal hydrogen chloride to decompose the lead salt) and the outcome of these investigations was to indicate the absence of nitrogen and, in the case of Heise's work on the bilberry, to recognise that glucosides constitute at least a part of the colouring substances.

Griffiths in 1903 obtained crystalline colouring matters from the scarlet pelargonium and verbena flowers, but his record of their composition and properties was quite erroneous.

Molisch (1905), who was a botanist, described crystalline anthocyanins (a term introduced by Marquart in 1835) *in situ* and gave readily followed instructions for the preparation of such substances outside the plant, although on a small scale. He expressed the view that the anthocyanins were glucosides. Grafe (1906—11) repeated Molisch's experiments on a large scale and in the case of the scarlet pelargonium had in his hands at one time no less than 10 g. of crystals. The formula, $C_{18}H_{26}O_{13}$, which was advanced for this material bears no obvious relation to the truth, though the analyses on which it was based were not necessarily incorrect. Presumably the material was a salt and the nature of the acid was not ascertained.

When Willstätter left Zürich for Berlin he took with him Arthur E. Everest whom he describes as an indefatigable collaborator. Their first paper on the anthocyanins in general, and the cornflower pigment in particular, established the main lines of the subsequent investigations. Unfortunately the cornflower proved one of the most intractable of sources and gave much more difficulty than its successor in the laboratory. It was shown that the pigment in the flowers was a blue potassium salt * and that the free colouring matter is violet. The red form obtained on addition of acid was recognised as an oxonium salt, and the anthocyanins were found to be most stable in this red salt form. In solution at appropriate pH many anthocyanins are decolorised. Willstätter and Everest found that this was due to *pseudo*-base formation and were able to restore the colour by the addition of acid. As already stated, concentrated aqueous solutions of the pigment were fractionally precipitated by alcohol and the process was repeated several times. The blue product was converted into the chloride by dissolution in alcoholic hydrogen chloride, and the salt fractionally precipitated by ether. The amorphous product was crystallised by slow evaporation of an aqueous-alcoholic hydrochloric acid solution.

The blue salt from the earlier stages was found to be a potassium salt and this was later obtained in fine hexagonal tablets.

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* Strictly speaking this is not quite exact. It was shown that the potassium salt could be obtained from the flowers. The pH of the sap is on the acid side of neutrality and the actual condition of the pigment is influenced by the presence of colloids and surfaces.

The crystalline chloride was called cyanin chloride and proved to be a diglucoside of cyanidin chloride. The hydrolysis could be effected by short boiling with 15—20% hydrochloric acid, and the glucose could be estimated after removal of the insoluble aglycone, cyanidin chloride. This was the first of the sugar-free salts to be isolated; the generic term is " anthocyanidin."

Willstätter and Everest found that amyl alcohol extracted cyanidin chloride completely from aqueous acid solution but only a small proportion (1·8%) of cyanin chloride, the beginning of an extremely useful practical method of separation and identification.

Monoglucosides, rhamnoglucosides, and acyl glucosides were later encountered and each had its characteristic distribution number, which is the percentage that passes to the amyl alcohol under standard conditions. Diglucosides gave distribution numbers of about 1—2, monoglucosides from about 8 to 40, rhamnoglucosides about 5—10, and some acyldiglucosides as much as 50—60. Willstätter and Everest ascribed the formula $C_{28}H_{33}O_{17}Cl,3H_2O$ to cyanin chloride and $C_{16}H_{13}O_7Cl$ to cyanidin chloride, but stated that they were not satisfied, since further analyses had given lower figures for carbon. Further investigation was promised. In the meantime a comparison was made with brazilein, $C_{16}H_{12}O_5$, and hæmatein, $C_{16}H_{12}O_6$; it seemed that cyanidin base could be the next member, $C_{16}H_{12}O_7$.

However, this speculation was soon abandoned with the extension of the research, from which it transpired that cyanidin chloride is $C_{15}H_{11}O_6Cl,H_2O$ and other anthocyanidins were later found to be based on C_{15}, or if not to contain methoxy-groups. The necessary correction was made in 1914.

Willstätter showed admirable intuitive judgment in his choice of flowers for examination. He found that he had been greatly helped by the florists whose selection and improvement of garden varieties had resulted in a large increase of the percentage of pigment. Occasionally it was as much as 20% of the weight of the dried petals. In such cases much simpler methods were feasible. For example, the deep red dahlia affords cyanin chloride by a method which is little more involved than a direct crystallisation from aqueous-alcoholic hydrochloric acid.

Among the more important contributions were those of Willstätter and Nolan (1915) who isolated cyanin chloride, $C_{27}H_{31}O_{16}Cl$, from the petals of *Rosa Gallica*, of Willstätter and Bolton (1915) on pelargonin chloride, $C_{27}H_{31}O_{15}Cl$, from the scarlet pelargonium, and of Willstätter and Mieg (1915) who obtained delphinin chloride $C_{41}H_{39}O_{21}Cl$ from the wild purple larkspur. Pelargonin gave pelargonidin chloride, $C_{15}H_{11}O_5Cl$, and two molecules of glucose, on hydrolysis with 20% hydrochloric acid, whilst delphinin chloride * similarly afforded delphinidin chloride, $C_{15}H_{11}O_7Cl$, along with two molecules of glucose and two of *p*-hydroxybenzoic acid. The three anthocyanidins, pelargonidin, cyanidin, and delphinidin were joined by certain methyl ethers, such as peonidin (*O*-methylcyanidin), but no new fundamental type was encountered in Willstätter's work, provided we exclude the nitrogenous anthocyanins which are mentioned below.

The first monoglucosidic anthocyanin to be isolated was oenin chloride, $C_{23}H_{25}O_{12}Cl$, from the skins of purple-black grapes (Willstätter and Zollinger, 1915—16). On hydrolysis this gave oenidin chloride, $C_{17}H_{15}O_7Cl$, which is now recognised as a type of very common occurrence. It proved to be a dimethyl ether of delphinidin chloride and could be converted into that substance by demethylation with hydriodic acid in the presence of phenol and treatment of the resulting delphinidin iodide with silver chloride. This anthocyanidin is now termed malvidin chloride; it was also obtained by hydrolysis of malvin chloride, a diglucoside from *Malva sylvestris* L. (Willstätter and Mieg, 1915).

Willstätter and Burdick (1917) separated the diglucoside, petunin chloride, from petunia hybrids (Karlsruher Rathaus) and found that the anthocyanidin was a monomethyl ether of delphinidin. Previously the colouring matter of the paeony had been recognised by Willstätter and Nolan (1915) as a diglucoside of a monomethyl ether of cyanidin. The constitutions of these methyl ethers were established by degradative and synthetic studies by later workers and Willstätter described malvidin under more than one name Ampelopsidin, for example, has no separate existence. However the work on petunidin has been fully confirmed by synthesis.

A further development was the isolation of an isomeride of cyanin from the common red poppy (*Papaver rhoeas*). This mecocyanin was purified through the sparingly soluble ferrocyanide. The monoglucosides of pelargonidin and cyanidin were found together in the aster (with Burdick, 1917), and the latter in chrysanthemum flowers (with E. K. Bolton,† 1917).

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* The true analogue of cyanin in the delphinidin series is delphin chloride, $C_{27}H_{31}O_{17}Cl$, later isolated by Scott-Moncrieff and the Lecturer from *Salvia patens*.

† Later Director of Chemical Research, Dupont Nemours & Co., Wilmington, N.J. The photograph reproduced facing p. 999 was taken by Dr. Bolton in the period of the anthocyanin work, and the Lecturer is very grateful to him for copies of it.

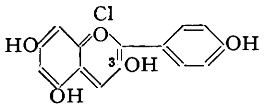
The Lecturer is proud of his small association with Willstätter in a paper claiming the identity of asterin and chrysanthemin. The crucial comparison of both specimens with the synthetic anthocyanin was performed in his presence at Manchester University and consisted in a determination of the distribution ratio. His scrutiny of the microscopic sediment in the 10-c.c. flask and the gesture accompanying " You can take it now " is well remembered. Chrysanthemin was also obtained by partial hydrolysis of mecocyanin. A monogalactoside of cyanidin was found in the cranberry (with Mallison, 1915); it was termed idaein. Rhamnoglucosides of cyanidin (with Zollinger, 1917) and delphinidin (with Weil, 1917) were also purified. The former was found in the skins of cherries and plums, and the latter in *Viola tricolor.* It is probable that Willstätter's keracyanin and prunicyanin are identical with each other and also with Scott-Moncrieff's antirrhinin from red snapdragons.

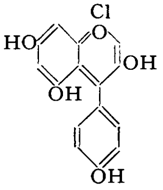
When the C_{15} skeleton of the anthocyanidins was established, the relation to the flavones and flavonols became apparent, especially as fusion of the anthocyanidins with potash had afforded phloroglucinol in every case and *p*-hydroxybenzoic acid, protocatechuic acid, and gallic acid from pelargonidin, cyanidin, and delphinidin respectively.

The salts were clearly pyrylium salts, the oxygen analogues of the pyridinium salts, and a group which had been established by Werner. Willstätter did not refer to this but always quoted Decker whose work of 1907 was more familiar to him. It was indeed more strictly applicable since it concerned benzopyrylium salts, whereas Werner's were dibenzopyrylium salts.

For pelargonidin chloride the two constitutions (XXXIX) and (XL) were suggested in 1914 as possible. Here the *o*-quinonoid structure was given preference in harmony with a suggestion by Perkin and the Lecturer. It may be that (XL) showed a lingering influence of the brazilin structure. Decisive evidence in favour of the flavylium structure (XXXIX) was provided by the reduction of quercetin to cyanidin (with Mallison, 1914) which was accomplished by magnesium in aqueous-methanolic hydrochloric acid. There results a relatively large proportion of sparingly soluble cyanidin-like material, probably derived from a pinacol, and about 4% of pure cyanidin chloride. The validity of this work was challenged by Nierenstein on insufficient grounds; the Lecturer was able to reproduce the results in every detail.

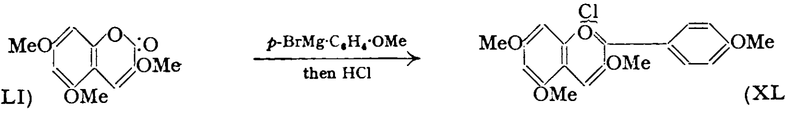
(XXXIX)





(XL)

The siting of the hydroxyl group at position 3 followed from the non-identity of cyanidin chloride with luteolin hydrochloride. The constitution of pelargonidin (XXXIX) was confirmed by a synthesis (with Zechmeister, 1914), eventually extended to that of cyanidin (with Zechmeister and Kindler, 1925). Phloroglucinaldehyde was condensed with sodium methoxyacetate and methoxyacetic anhydride to a coumarin derivative which was hydrolysed and methylated to 3 : 5 : 7-trimethoxycoumarin (XLI). This reacted with *p*-methoxyphenylmagnesium bromide to give a *pseudo*-base from which pelargonidin tetramethyl ether chloride (XLII) could be obtained. The final stages were demethylation with hydriodic acid and conversion of pelargonidin iodide into pelargonidin chloride.



(XLI) (XLII)

Willstätter has told us that the enforced cessation of his anthocyanin work gave him great pain. His memory of Dahlem was chiefly of flowers and their colour, but after the outbreak of the first Great War he was unable to continue his labours of love.

The team was dispersed and the flowers went to the hospitals. He then became engrossed in the study of enzymes and never attempted any further work on flower pigments. P. Karrer made important contributions especially by the discoveries (with Widmer, 1927) of hirsutin in *Primula hirsuta* which gives on hydrolysis a new trimethyl ether of delphinidin (3′ : 5′ : 7), of monardaein from *Monarda didyma,* which is a complex derivative of pelargonin affording *p*-hydroxycinnamic acid on hydrolysis, and of gentianin from *Gentiana acaulis,* which gives on hydrolysis one molecule each of delphinidin, glucose, and *p*-hydroxycinnamic acid.

The Lecturer developed the synthetic method which he had discovered in 1906 when working with Perkin. This is the same method as that of Decker whose work was simultaneous and independent.

By various refinements of technique and preparation of the most suitable intermediates this general synthesis, the condensation of salicylaldehydes with ketomethylene compounds, was found capable of fulfilling all requirements, and all the anthocyanidins as well as many anthocyanins were synthesised. Having squatted on the property it was satisfactory, as well as a great honour, to receive a legal title in the appointment of residuary legatee, which was contained in the foreword to the collected papers on enzymes (1928). No attempt can be made to describe the later work on anthocyanins. Once again the identity of synthetic cyanidin chloride with the product from natural sources was questioned by Malkin and Nierenstein (1928).

The preparations from both sources were kindly repeated by Prof. R. Kuhn and by Dr. T. Wagner-Jauregg, who found that they were identical (1928). Other relations of importance are the catalytic reduction of cyanidin to ($\pm$)-*epi*catechin (Freudenberg, 1925), the conversion of (+)-catechin into cyanidin (Appel and Robinson, 1935), and the reduction of flavonols to anthocyanidins by lithium aluminium hydride (Mirza and Robinson, 1950). Willstätter and also Everest, in this case independently, were interested in the possible relation of anthocyanin and anthoxanthin pigments in flowers but there does not appear to be much statistical evidence in favour of this relation interpreted in its most direct sense. It seems more probable that flavonol and anthocyanin are produced in parallel, probably along the same path for a part of the way. Very little is known with certainty in the field, but genetic studies by Scott-Moncrieff and Lawrence favour this hypothesis, and moreover the co-existence of related anthoxanthins and anthocyanins is the exception rather than the rule.

The three main types, so quickly uncovered by Willstätter and his colleagues, remain and the small number of exceptions proves the rule. A rather complete survey of anthocyanins made in collaboration with Lady Robinson and J. R. Price has only brought to light one new type, namely, gesnerin from *Gesnera fulgens* which is related to apigenin. The colour-base of such an anthocyanidin lacking the hydroxyl in position 3 is also recognisable in carajurin, a cosmetic pigment used in former times by denizens of the Orinoco (A. G. Perkin, Chapman, and Robinson, 1927) and is probably derived from the anthocyanin of a species of *bignonia*.

Willstätter was aware that new anthocyanins occurred in certain papaveraceae, *e.g.*, *Papaver alpinus*, and another probable source of new types is the young fern frond (Price, Robinson, and Sturgess, 1938). But the chief novel type is that of the nitrogenous anthocyanin which Willstätter recognised in the beet pigment, in *Atriplex*, and in *Celosia*.

He started work on betanin from *Beta vulgaris* but it is doubtful what relation the product obtained had to the original pigment. A novel method was worked out for this purpose, namely, extraction with a mixture of amyl alcohol, acetophenone, and dichloropicric acid. The only description available is in a thesis by Schudel. Eventually betanin or a degraded pigment, or an ethyl ester of either, was crystallised and analysed. The results showed that two nitrogen atoms were contained in the molecule. Work at Oxford (with Ainley, 1937) confirmed the nitrogen content and has now been resumed.

The Lecturer is aware that this account of Willstätter's researches on flower pigments is very incomplete but it is necessarily so on account of the rich content of his work. Almost everything would be worthy of mention.

Miscellaneous Chemical Studies.—Very early in 1893, Willstätter prepared *cyclo*pentenecarboxylic acid by the action of alcoholic sodium ethoxide on ethyl $\alpha\alpha'$-dibromopimelate. The reaction is similar to the well-known method of formation of caronic acid from ethyl bromodimethylglutarate. It could not be extended to the *cyclo*hexane series. The catholicity of his interests emerges from the following list of topics. Action of sodium on ethyl malonate (continuation of work initiated by Baeyer); derivatives of diaminoacetic and malonic acids; formation of a hydrocarbon, $C_{12}H_{16}$, from quinitol (with R. Lessing); syntheses of hygric acid, ecgonic acid; ornithine and other amino-acids; hydrogen peroxide of crystallisation; the action of hydrogen peroxide on sodium thiosulphate; the separation of gold from platinum (ether quantitatively extracts the gold chloride and no platinic chloride from an aqueous solution); the theory of dyeing; use of Caro's acid; several papers on betaines (observation of wandering of alkyl from oxygen to nitrogen); lecithin; estimation of glycerol in fats; sparteine; pyrones; thioformamide; calcium and magnesium content of seeds; estimation of small quantities of iron; reduction of lignin and carbohydrates by hydriodic acid and phosphorus; alkalimetric estimation of amino-acids and peptides; volumetric estimation of acetylene; vinylacetylene; hydrolysis of cellulose.

We may pause here to remark that this work with Zechmeister on cellulose in 1913 has been made the basis of a technical process. E. Berl (1942) has remarked that the so-called Bergius process for the saccharification of wood should be called the Willstätter process. The fundamental observation was the rapid dissolution of cellulose by hydrochloric acid containing 40—41% of hydrogen chloride in contrast to the slow action of the usual concentrated acid. With Duisberg in 1923 he studied the preparation and pharmacological properties of trichloro- and tribromo-ethyl alcohol, which have found uses in practical medicine as narcotics.

To resume, he also wrote on indigoids from halogenated naphthols (interesting in colour photography); nitrourea; the rearrangement of naphthaquinone phenylhydrazones; acetone compounds from α-hydroxy-acids; the constitution of purpurogallin; and, strange to say, on the blue colour of sea water. This is worth noting because it is the unique instance of a Willstätter speculation not backed by his own experimental work. He thought the colour might be due to copper ammines.

Research on Enzymes.—The Lecturer wlll attempt only a brief review of this work, partly because he is not competent to estimate its net value or to appraise the relative significance and promise of different sections of the voluminous records. He is very unhappy to be under this necessity because it is so obvious that Willstätter himself attached the greatest possible importance to this phase of his life's work. His first contact with the new interest was probably concerned with chlorophyllase to which reference has already been made. Then from 1918 onwards he was actively engaged with a large number of collaborators in investigating the purification and properties of a variety of enzymes including glucosidases, lipases, proteinases, and peptidases, and the peroxidase of horseradish. His co-workers included A. Stoll, R. Kuhn, E. Waldschmidt-Leitz, and K. Linderstrøm-Lang, to mention only a few of those who have taken the highest rank among chemists and contributed much to biochemistry. The chief resource for the separation of many enzymes was adsorption on alumina, silica gel, or other solid adsorbent with subsequent elution at different pH's or with other change of solvent.

With characteristic thoroughness he studied the preparation of suitable adsorbents in great detail. For example, in the case of aluminium hydroxide, four different primary products were distinguished according to the method of precipitation and these had different uses. The meta-compound, AlO_2H, was found to have the most selective action as adsorbent. It has indeed been found possible to separate enzymes from one another by adsorption. The pancreatic mixture of lipase, trypsin, and amylase was an early example. Lipase was adsorbed by γ-alumina and afterwards the trypsin was taken out by kaolin. Amylase was the most resistant to adsorption. Unfortunately his methods of purification, though they appeared to give startling increases of activity (×1000 and more) were not really adequate for the full purpose. They have nevertheless been of immense service to subsequent investigators. Willstätter was obsessed by the idea that the enzymes consisted of some active substance, possibly of relatively small molecular weight, associated with a protein or other macromolecule. As the stability of his preparations decreased with increased activity, he was led to believe that the isolation of the active moiety was not possible. There was enough difference between this conception and the modern view to make it unlikely that he could have hit on the truth that the enzymes are proteins themselves and that, if there is a localised active group, it is a part of the protein molecule. He did, indeed, discuss this conception. So far as the Lecturer is aware he did not even try to crystallise an enzyme and that was due to his preconceived, or perhaps better, his growing conviction that they were not chemical substances, but chemical systems.

Nevertheless he was able to make fundamental contributions to our knowledge of the general properties of enzymes and to their accepted interpretations in terms of specificity, competition of substrates, competition of inhibitors with substrates, activators, non-competitive inhibition, and effects of changes of temperature and pH. The crystallisation of certain proteins, including physiologically active ones like insulin, followed by the crystallisation of recognised enzymes by Sumner (1926), and by Northrop, showed that Willstätter's working hypothesis was incorrect, though he himself remained unconvinced. A definite disadvantage of his theory was that it made it impossible for him to distinguish chemically between enzyme and impurities of a similar nature. Although therefore we must be grateful for an immense amount of spade-work which facilitated the labours of others and made real contributions to knowledge, the glittering treasure was not uncovered.

The Faraday Lecture of 1927 was entitled " Problems and Methods in Enzyme Research " and a perusal of this shows how near Wlllstätter came to the position we now consider to be correct. " There is no sure method available for freeing the enzymes from the protein derivatives. However, if a certain enzyme in isolated cases could be freed quantitatively from accompanying proteins this might be considered a sufficient demonstration that this enzyme neither is protein nor requires protein for its activity. Nevertheless the tenacity with which proteins cling to enzymes has threatened again and again to impose the conclusion that the enzymes are of protein character." Finally it should be noted that Willstätter did not regard all his colloidal carriers as proteins and it would perhaps be unwise even now to declare that all enzymes are proteins, unless we make them such by definition.

Willstätter was inclined to think it not improbable that his ancestors came to Germany with Roman Legionaries but his real knowledge starts with his grandfather's greatgrandfather, known as Rabbi Ephraim, who came from the Alsatian country of Hanau-Lichtenberg to Karlsruhe. His grandfather was a doctor and his father Max (1840—1912) was the eldest of five children. After an apprenticeship in the wool trade he went to England and worked for several years in Nottingham. In 1870 he married Sophie, the daughter of a prosperous wool merchant, but in 1883 went to New York and, as his son has recorded with candour, not only in the hope of improving his finances but also to escape the boredom of Karlsruhe. He left Richard with his mother in Nürnberg and stayed away for no less than seventeen years. He was a handsome and lively man and returned at the age of 60, somewhat tired by toil and trouble, too fond of smoking, and with a weak heart. In 1900 Willstätter's parents came to Munich and he rejoined their household until his marriage. Willstätter's father, who helped his son by copying manuscripts, lived for ten years after his return from America, and his mother for sixteen and a half years longer. She died in 1928 and hence saw the triumphs of her son's career.

Richard was born at Karlsruhe on August 13th, 1872, and the first ten years of his life were spent there in very much the same way as by other intelligent children with happy homes and interesting surroundings. At the age of six he made a collection of minerals and at twelve he was quite sure that he wanted to study chemistry, but this was a spontaneous decision and nobody seems to have given him the slightest encouragement or direction. When he was only a little older he experienced the effects of anti-semitism. Groups of urchins in Karlsruhe attacked with abuse, and even stones, a Jewish child who ventured to walk alone. Although he escaped brutal punishment himself, his account of the school that he attended in Karlsruhe reads like a chapter of " Nicholas Nickleby." In 1881 he entered the gymnasium, described as an excellent institution beautifully situated near the forest, but his first few months were unhappy, chiefly because he was quartered with an aunt who lived in somewhat poor circumstances " principally on potatoes and somewhat bad ones." But this was only occasioned by the scarlet fever of his brother and all was well when he returned home and his report stated " apparently trying to improve his writing."

After the move to Nürnberg he was again less happy; he found the school requirements severe, his teachers unfriendly, and the anti-semitism more acute than in Karlsruhe. In Nürnberg it was no longer a question of hooligans but of the middle class, the sons of professional men and shopkeepers. He was depressed too by his unusual family circumstances, the inexplicable absence of his father—and they made fun of his dialect. Progress at school was slow except in arithmetic, history, and geography. But Latin was much more important and this was far from being his favourite subject. A family council decided to transfer him to the Realgymnasium with a view to a commercial career; at the same time his brother was to haunt the academic groves.

But soon he began to study chemistry and it was his brother who became a business man ! He stayed six years at the Realgymnasium where he was fortunate to come under the influence of enthusiastic teachers, far superior, he said, in their sense of duty to any he later encountered in University life. One gathers from " Aus meinem Leben " that the young Willstätter was a very thoughtful but introspective boy, he could not understand why proficiency in science made him unpopular with his school-mates, whereas achievement in sport or singing was always applauded. And he goes on to reflect that " some nations do not sufficiently understand that wars are won, not only by strengthening the health and vigour of the masses, but much more by individual intellectual achievements in the preparation and conduct of the war." Which nations could he have had in mind ? About the middle of this period he became desperately ill with diphtheria which attacked the central nervous system and produced widespread paralysis. There was little hope of recovery but he rallied and after six months rejoined his classes, only to become a victim to scarlet fever, followed by inflammation of the kidneys. This was his last serious illness.

A little later he joined the Unterprima and Oberprima and for the first and last time took full part in the dances, drinking bouts, and smoking concerts which were obligatory and a kind of immature imitation of what these young students thought went on in the Universities.

When he entered the Oberprima he made his first holiday trip alone and thoroughly conquered Upper Bavaria, both the cities and the mountains. Never before or since, he writes, did I have such a glorious time.

As a result of the Final Examination he was recommended for admission to the Royal Maximilianeum, a beautiful, well endowed Institution where a number of graduates from Bavarian schools were given special help to further their studies.

On the ground of religion only, the application was refused.

With strong leanings towards medicine which curiously enough were evinced as late as his early Zürich days,* he had early decided to devote himself to chemistry and went to Munich in October 1890 to study at the University and also to attend lectures at the Technische Hochschule. Here he found a little living room, which was clean and neat, and was generally looked after by an uncle, Emil Ulman, only two years his academic senior and a law student. His companions, partly for this reason, were all older than himself; they never discussed their studies, and posed as men of leisure. Very soon he decided to give up regular social distractions and to work harder than heretofore. Nevertheless he continued a very broad course of study and took full advantage of his opportunities for wide reading, conversation, and attendance at the opera, the theatre, or the thrilling Lieder recitals of Hermine Spies.

In his first year he attended far too many lectures and was not impressed by their quality. He was also pained by the " indescribably disturbing and merciless behaviour of those medical and pharmaceutical students who attended scientific lectures."

We seem to have heard of analogous phenomena in other places.

At the Technische Hochschule a leading teacher was Dr. K. Daniel, and Willstätter was privileged to help him in the preparation of large amounts of anhydrous prussic acid from potassium ferrocyanide. This was done on Sunday morning and one day he tried to replace the formula $Fe(CN)_2 \cdot 4KCN$ by a more modern one. Dr. Daniel saw his efforts in the notebook and was angry : " If you wish to waste your time with such trifles you should go to Professor Baeyer," he said. This advice was gladly followed.

On entering the laboratory in the Arcisstrasse he felt that all his difficulties lay behind him and he was happy to be on the straight road to his objective. In his second semester he had completed preliminary work and was ready for the organic laboratory but there was again no place for him.

He had passed an examination in analytical and inorganic chemistry and to his surprise was immediately examined by Baeyer in organic chemistry. He failed, but after a very short period applied for further examination and, although the Professor was surprised, he passed the candidate. There was still no place in the laboratory.

Then on a geological excursion the ill-equipped student lost his footing on a snowfield of the Sojen Mountain, was struck several times on the head, and in the side, but eventually escaped with broken ribs and an injured lung. His doctor was a young man called Stubenrauch who became a lifelong friend and who had himself a predilection for chemical experiments. For example, he noted a reaction between silver nitrate and iodoform with evolution of gas. This was identified by Willstätter as carbon monoxide. The reaction was earlier noted by Greshoff but the name of Stubenrauch also appears in the appropriate place in Beilstein's " Handbuch."

After the accident he was visited by Professor von Zittel who reported to Baeyer and the upshot was that Willstätter was allowed to begin organic elementary analysis as a part-time worker pending full recovery. As a result of his accident he was unable to undertake military service and was declared fit for this purpose only twenty-five years later, when he had already been awarded the Iron Cross for non-combatants. At that time Professor Wieland was declared fit for garrison service but it was noted that he was of more value as a chemist. Neither of them was called up.

In his fourth semester he attended Baeyer's lectures and in the winter of the same year entered the main organic laboratory. He had intended to go to Würzburg where Emil Fischer's sugar work was attracting much attention. However an older student said to him : " Yes. Go to Würzburg, it is much easier to get a Doctorate there." Whereupon Willstätter decided to stay in Munich. There he came in contact with many chemists whose names are household words to us : Buchner, Rupe, and Bamberger were among those who taught him in the early years. In February 1893 he applied for the pre-doctorate examination and after taking it wandered about the laboratory not knowing what fate had in store with him. He longed to

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* And even later. He was fond of prescribing for his friends : either calcium gluconate or one drop of tincture of iodine in a tumblerful of water.

work with Baeyer but was instead assigned to Alfred Einhorn with results which have already been described.

His growth in stature in the chemical world early became obvious to Baeyer who paid him special attention and became his friend. He often entered the master's laboratory where W. Dieckmann and then for many years the loyal Victor Villiger worked as private assistants. He watched Baeyer's innumerable test-tube experiments, often consumed with doubt about the progress of his own, until the dinner gong sounded once, and a second time more urgently. He wondered whether he could simulate Baeyer, but the verdict was that he could not adopt the same methods; he had to work out his own salvation. However he learned to know the great man, for whom he had so much admiration and respect that there was less room for warmth of affection.

In 1893 Johannes Thiele succeeded Bamberger as Associate Professor and head of the Organic Department and Baeyer offered Willstätter, then twenty-two years of age, a post as private assistant to Thiele and, when this proved unacceptable, to himself. This was also refused with some trepidation but Baeyer was not in any way annoyed and approved the plan to study cocaine by way of tropine.

For highly interesting recollections of J. Thiele, E. Buchner, W. Königs, V. Ipatieff, M. Gomberg, F. Blau, P. Walden, and many others, reference must be made to "Aus meinem Leben."

Independent work started in 1894 and in 1896 he became Privatdozent. This position had its minor drawbacks. In order to keep his student place he had to sign up and pay for the organic practical course, year after year, until he succeeded Thiele as Professor extraordinarius. Moreover, the balances were assigned by the section head and he not only got a bad one but had to share it with seven or eight young students.

The combustion furnaces had to be started at 10 a.m. and failure to do this involved a fine of 50 pfennigs. On one occasion Willstätter was fined and as he refused to pay the matter was reported to Baeyer. The defence that he had finished a combustion *before* 10 a.m. was considered adequate.

The trip to America, already mentioned, included visits to New York, Boston, Philadelphia and Niagara Falls. It must have been a pleasant interlude but he was itching to get back to his two keys to the tropine work and was able to do this about January 1896.

As a Privatdozent he gave six or seven courses of lectures of which one on " homology " was especially appreciated by the students. It was a course on aliphatic chemistry supplementary to Baeyer's own lectures. During this period as Privatdozent, Baeyer's friendship, the greatest personal experience of his youth, cooled off. He congratulated Willstätter on two of his papers at an interval of a year and each time added : " But you must become a Christian." With him the doctrine of assimilation was firmly entrenched whereas Willstätter came of a community that remained faithful to Judaism and sought freer development in emigration rather than in assimilation.

In 1899 it seems that there was some question of an Associate Professorship and Baeyer called Willstätter to his country house at Sternberg in order to communicate " important news." There was a scientific discussion but no news. This must have been a grievous disappointment since he had received the premature congratulations of the mineralogist von Groth. A few days later it was announced that the post had been awarded to Piloty, who was Baeyer's son-in-law. According to Willstätter, the cabinet of the ladies had been victorious overnight, but he fully approved the appointment of Piloty. In his fifth year as Privatdozent the tropine work had reached such a stage that Willstätter's scientific position was assured. Baeyer came to his laboratory, sat down, and remained silent for some time. Then he said " My dear Willstätter, what do you want to do now ? You cannot get a chair and in industry there is no place for you." The reply was that Willstätter would be very pleased to continue working in the Institute. A fortnight later he had a most attractive offer of a Directorship in a rather large North German concern. This was declined but Baeyer thought he should have accepted. The Lecturer has dwelt on all these early difficulties because they demonstrate the indomitable spirit of the man, his courage, patience, fortitude, and self-control.

In the winter semester of 1901—2 Thiele was called to Strasburg and in the Spring of 1902 Willstätter became his successor as Head of the Organic Section and Professor extraordinarius although delay in ratification meant that full duties were not assumed until the Autumn. There was even some difficulty about that and he refused the offer of only the first half of this assignment, the situation being saved when the Ministry stepped in with a ruling that the chair must be filled or allowed to lapse. The trouble had been that the senior professors hoped to extend their privileges by not appointing any more Associate Professors.

On appointment Willstätter had to be formally presented to the Prince Regent Luitpold, and Baeyer offered him his court uniform. The difference in measurements would have made the spectacle worth witnessing. This time he was fortunate—academic robes were ruled to be in order.

Many years later, in Oxford, he received an Honorary Doctorate, and dined with Perkin at Magdalen College. His housekeeper had told him to pack a " smoking " but Willstätter said that he had been in Cambridge and was sure it would be unnecessary. But he had made insufficient allowance for local customs in the ancient Universities. Perkin dressed him in an old dinner jacket of his own and it was with great feeling that Willstätter exclaimed to the Lecturer : " This was the most miserable experience of my life." An exaggeration, but he was habitually dapper and neat.

A lecture course to which great importance was attached was that on the synthetic dyes and Willstätter prepared himself for this by a summer visit to the Badische Anilin and Soda Fabrik at Ludwigshafen where he was the guest of the Directors. He made a collection of dyeings and printings for use in the lectures, but, more important still, he met such masters as Paul Julius and René Bohn and learned much of the chemistry of azo-dyes and anthraquinone. But he did not enter the production sheds and was forbidden contact with the chemists. A member of the patent section was detailed to look after him at meal-times.

The improvement in Willstätter's working conditions after his twelve years' apprenticeship was astonishing; he shared the services of a laboratory cleaner assistant with Baeyer and Königs, and was able to work on Saturday afternoons and Sundays ; the privilege of the laboratory latchkey. It was not long before a steady stream of students came to work with him, and such topics as the later tropine work, the quinones, quinonoid dyes, and cyclic hydrocarbons were attacked. A beginning was made in the chlorophyll field for Willstätter records that before he left Munich he knew the secret, presumably the magnesium content, and that for him the green countryside had a message which nobody shared.

The call to Zürich was the occasion for a jolly party in which Baeyer made his usual happy speech. Placards denoting Willstätter's achievements (and hopes) appeared and a telegram arrived " Switzerland renames Vierwaldstättersee, vierwillstättersee."

Willstätter had no hobbies in the usual sense of the term but he was fond of walking in fine country and often with companions from the laboratory. In order to help with the delivery of early morning lectures he seems to have deliberately taken up riding and found this very much to his taste. From Interlaken he rode into the Lauterbrunnen Tal or as far as the upper Grindelwald glacier.

An American cousin of his mother's lived in Wiesbaden and kept some good saddle-horses and there was a standing invitation which was taken up in the Easter vacation of 1903. But as the result of a domestic tragedy, Willstätter went to a hotel and in the lobby met the dignified, long grey-bearded figure of Professor Leser of Heidelberg and was invited to his table. Then and later in the evening he met for the first time the Professor's charming daughter, Sophie. A few weeks afterwards they were engaged and married in the summer. His son Ludwig was born at Munich in October 1904 and his daughter Margarete was born in Zürich at the time when Willstätter was writing his paper on the magnesium complex of chlorophyll. Margarete showed considerable mathematical talent and published some original papers, partly under the guidance of Sommerfeld. After the marriage to Dr. Ernst Bruch they went to the United States and a son, Ludwig Willstätter Bruch was born in January 1940 at Winnebago, Illinois. It was on receipt of this happy news that Willstätter decided to write his memoirs and in the foreword says that his grandson shall take the place of his lost friends and students.

In June 1908 his wife died after a delayed operation for appendicitis. The disaster was stunning and following it Willstätter took not a single day's holiday in ten years. Sophie Willstätter was cultured and beautiful; though not trained as a chemist she tried hard to understand her husband's work and attended many of his lectures. Shortly before her death the Lecturer had arranged to work under Willstätter at Zürich but in August 1908 Willstätter wrote that he did not wish him to come because he was heartbroken and felt that in the circumstances he would be unable to give detailed supervision. A quite different account is given in " Aus meinem Leben " which it should be noted was largely written from memory.

And this is how he closes the Chapter in which his bereavement is recorded : " Without mercy life continues, hideous in its conquering strength. I returned to the lecture room. The empty seat next to Mr. Schuppli glared at me. Yet my children must not grow up in a house of mourning. They had a right to happiness. I took the place of their mother."

The scientific record of Zürich is almost unique, as a few of the names of those who worked there will quickly show—a list at haphazard—J. Wislicenus, Victor Meyer, Lunge, Bamberger, Bredig, Werner, Willstätter, Debye, Einstein, and now Karrer, Ruzicka, and Prelog. The favourable atmosphere was certainly due to the wisdom of such men as Johann Karl Kappeler and Robert Grehm who established a most liberal tradition The last-named, formerly a Professor of Chemical Technology and in Willstätter's time Chairman of the Board of Education, proved a good friend and saw to it that the temporary appointment was made permanent, that his salary was increased, and that additional funds were made available to meet heavy expenditure on research. According to Willstätter the Swiss students were more serious-minded than the German. Jokes or anecdotes were taboo and they expected a complete account which would save them the necessity of purchasing a textbook. The lectures on both inorganic and organic chemistry were illustrated by numerous experiments which were very carefully prepared, and the arrangements were inspected on the previous evening.

Willstätter has given admirable pictures of his Zürich days and portraits of his friends and colleagues including Alfred Werner at the University but, although these matters are of high general interest, they have only a secondary importance in relation to our present topic.

The anthocyanin work was started in Zürich with Everest using cornflower petals obtained from the firm of E. Merck in Darmstadt. *Flores centaurae cyanus* played a significant part in old herbals. This material contained only about 0·5% of colouring matter. At Dahlem dark purple cornflowers were grown and these contained 12—13% of pigment in the dried petals. As delegate of the Swiss Board of Education Willstätter made several trips abroad, for example, with Werner to the Jubilee of the French Chemical Society and to the Centennial of the University of Berlin in 1910. At this brilliant ceremony the Emperor announced the formation of the Kaiser Wilhelm Gesellschaft zur Förderung der Wissenschaften. Emil Fischer received the title of Excellenz and told Willstätter of the plans for the K. W. Gesellschaft.

In 1911, after nibblings from Würzburg and Vienna in 1910, Willstätter received a call to the new Institute which he declined because the conditions were held to be unsatisfactory. After Fischer had visited Zürich with powers to attract Willstätter by much better offers, the post of Director was accepted, the main factor being that he felt himself to be a German.

The Lecturer remembers an occasion when he took Willstätter by road from London to Oxford and when he explained this matter in detail. It was after his resignation from Munich and yet he said with considerable elaboration " Einstein is a German Jew; I am a Jewish German." The Institute building was not dedicated until October 1912 and the outbreak of war in August 1914 marked the end of normal working conditions.

The Dahlem period was thus not much more than twenty months. Although the two had met previously this time marks the beginning of one of the strongest of Willstätter's personal friendships, that with Fritz Haber, Professor in Karlsruhe. Haber went to the second Kaiser Wilhelm Institute for physical chemistry, in 1911. Frequent scientific collaboration of these close friends was not to be expected, but they did publish one paper together on the mechanism of oxidation. This was concerned with the rôle of radical chains both in inorganic processes and in certain enzymic oxidations.

Fischer had held out the prospect of complete freedom. Go walks if you like; be idle for a year or two, if you wish, and meanwhile think out some new ideas. But shortly after reaching Berlin he was invited to the house of an eminent Astronomer (Nobel Prize for 1920) Karl Schwarzschild who had been a fellow member of the Privatdozentverein at Munich. Late in the evening Schwarzschild, who was a member of the Administrative Committee, said in measured tones : " We did not bring you here to attend parties. We expect good things from you and quickly."

The anthocyanins provided these results and as quickly as anyone could wish.

In other respects Willstätter found that promises made to him were not fulfilled to the letter. He did not receive a title which he had been led to expect, that of Geh. Regierungsrat (this came on his transference to Munich) and his budget was inadequate and had to be supplemented from his own pocket. This certainly suggests that Willstätter's means must have been above the professorial average. On the day of the dedication he was asked by a high-ranking Berlin personality : " How do you manage to live in such a tiny house ? "; whereupon the answer was that it was in proportion to his salary. Later he realised that His Excellency had mistaken the Hausmeisterkiosk for his villa, which had been built by Professor Breslauer. It was later acquired by a banker and still later housed the President of the Berlin Police.

Haber and Willstätter had some say in the naming of the new streets near the Institutes and Willstätter's house stood in Faraday Weg; very appropriate for a future Faraday Lecturer.

It is worth noting that the ground floor of the first Kaiser Wilhelm Institute was occupied by Professor Otto Hahn, who later became Director not only of one of the Kaiser Wilhelm

Institutes but also of its successor, the Max Planck Institute at Göttingen. The first floor was Willstätter's and the second was occupied by Prof. E. Beckmann's laboratory.

Not long before the outbreak of war Willstätter visited England and lectured on plant pigments at University College, London, in May. The next month found him in Paris at the General Meeting of the Société Chimique de France. He was asked at an evening party what people in Berlin thought of the prospects of war. He replied that he knew nothing about it, but was not believed.

In fact we are assured in " Aus meinem Leben " that the outbreak of war was to him like a catastrophic earthquake; it was thought that the cloud would pass. Willstätter's comments on these questions are of psychological interest and his conclusion cannot be unilaterally applied. " The guilt of the German people at the turn of the century and after was the low level of political talent, training, activity, and altruism."

Towards the end of 1914 Haber and Willstätter, whose offer of war service had been declined, became members of the Prussian Academy of Sciences and this was Willstätter's first opportunity to participate in the general scientific life of Berlin. It is interesting that Diels and Planck were among the Secretaries.

In 1915 Ludwig Willstätter died rather suddenly and apparently in a diabetic coma. He was ten years of age and a winsome child of much promise. Willstätter mentions that his impoverished life went on. The next weeks brought invitations from Göttingen, Munich, and Vienna, the next months were filled with work on gas protection for the armies, anniversary lectures, professional journeys, etc., and the award of the Nobel Prize (1915).

The appointment as Professor and Director of the State Chemical Laboratory in Munich was dated Sept. 4th, 1915. This consummation was not reached without troubles. For example, a salary was mentioned, but it was explained that the official residence could no longer be rent-free. Then the rent was assessed, after Willstätter had modernised the house, at an amount equal to his salary. This was eventually smoothed out by some arrangement about the fees. In addition Willstätter made many stipulations, many of them quite important ones, which were all accepted and led to a great improvement of the laboratories including a new Institute for Physical Chemistry.

At the beginning of his second period in Munich Willstätter was given proof of strong anti-semitism and this grew during the war and eventually led to his resignation.

The actual move to Munich was delayed a few months in order to allow time for certain laboratory improvements. In the meantime Willstätter developed a gas-mask filling, consisting of layers of carbon and hexamethylenetetramine. Thirty million containers with such charges were said to have been put in service and to have proved satisfactory. For this service he was awarded the order of the Iron Cross, Second Class; the recommendation for this came from various groups but was rejected by the Ministry of War until the Kaiser insisted.

After the war a telegram announced that the head of the British chemical warfare division, a certain General Hantley, would visit him. Willstätter was working at his desk when his visitor stood at the door, smiling, and was recognised as a former colleague, Hartley (Sir Harold, of course) who in 1898 had come to him as a student, attended his lectures, and visited his home.

When he arrived in Munich much energy was spent in reorganisation of the courses and laboratories and in building large extensions. These matters and the war involved a definite break with the past in the field of research.

The war itself forced a limitation of activities in Germany as in other countries. Even after the war it was hard to collect a " School " in the old sense; the best years were from 1921 to 1924.

His colleagues included many eminent scholars, among them Röntgen, von Groth, von Seeliger, von Goebel, Aurel Voss, Alfred Pringsheim, and Arthur Sommerfeld. Heinrich Wieland was for some time head of the Organic Division and other heads of divisions were K. H. Meyer and R. Pummerer but these were soon absorbed in war service and Willstätter found that in addition to his own responsibilities he had to assume those of several younger colleagues.

As already mentioned, Willstätter originally stipulated that a full Chair of physical chemistry should be instituted and a new Institute should be built. He was very concerned to see this implemented, though he makes the remark which will not be very palatable to many colleagues, and was not in fact true, that physical chemistry had passed its zenith.

Failing to get any satisfaction from the Ministry he decided to act and invited K. Fajans to enter his laboratory. This was a happy choice and in later years Fajans became a full professor of the University. With the help of the Rockefeller Foundation a fine Institute was erected but, soon after the rise of Hitler to power, Fajans left Germany as a refugee, to become Professor at the University of Michigan. In 1918 O. Hönigschmid also joined the Department. Arthur Stoll, who had acted as Willstätter's assistant in Dahlem, accompanied him to Munich and there continued the work on photosynthesis which seems to link the early organic chemical interests of Willstätter with the essentially biochemical pre-occupation of his later life. The first enzyme work actually dates from Zürich days when the distinguished Spanish organic chemist A. Madinaveitia helped to concentrate catalase in 1909—11.

Stoll undertook the extension of this work with success and took part in other enzyme researches, returning in 1917 to Basle to a scientific career in industry. His work as a director of the Chem. Fabrik Sandoz has not interfered with the development of his researches as may be seen from his outstanding contributions on ergot and the cardiac glucosides.

The Lecturer must pass over any attempt to describe the historic events at the end of the first world war or to analyse the causes of the growth of anti-semitism between the wars. Suffice it to say that Willstätter thought the desire to find a scapegoat led to the blame for many occurrences being placed to the account of the Jews.

Of the political events immediately following the first world war the only one which is a necessary part of our narrative is the action that Willstätter took to protest against what he considered the false picture of German conditions painted in a Swiss newspaper. This was a letter of protest entitled " Germany in Mourning " and there is very little doubt that his indignation was not unconnected with the inclusion of the name of Fritz Haber in the list of those accused of war crimes.

In common with other professional men Willstätter suffered great financial loss through the deflation but the laboratory was rescued by the very considerable dollar donation of a New York brewer, Theodore Haebler, who had a great regard for Willstätter.

An invitation to the chair of chemistry in Berlin was received in 1919 but this he declined after having received many protestations of the high esteem in which he was held by his colleagues in the Faculty at Munich.

The Nobel Prize celebrations for those awarded prizes during the war was held in June 1920. Those so honoured were Barkla, Barany, Planck, von Laue, Haber, Stark, and Willstätter. Willstätter seems to have spent much of his time preparing an address for the Anniversary Celebration of the founding of the Emil Fischer Gesellschaft but his Nobel Lecture was somewhat perfunctory. He was interested to meet Arrhenius, Hammarsten, and Widman, who with Baeyer solved the riddle of cymene, when Willstätter was still at school.

He then became Dean of the Faculty and was naturally much involved in general University affairs. Furthermore he made many journeys to Berlin, partly it is true to renew his friendship with Haber, but also on business of varied kind, industrial and official. He bitterly regretted the waste of time that this involved and indeed the problem is not unknown in other countries and, so far from being solved, tends to become more and more insoluble. In spite of these distractions Willstätter continued to do splendid work in organic chemistry and biochemistry and he attracted very many co-workers both German and from many foreign countries.

Willstätter was respected and admired by all members of the Faculty but it was a personal affection that was felt for him and general anti-semitism was rife and on the increase.

The trouble came to a head with the three Goldschmidts. When Pummerer left for Greifswald it entered the mind of the Director to appoint Stefan Goldschmidt in his place. This he did not do because of the urgent warnings of his friends, and other candidates were available.

In 1924 Professor von Hartwig, the geneticist, retired and by common consent the best candidate was Richard Goldschmidt, then associate director of the Kaiser Wilhelm Institute for Experimental Biology in Dahlem. But essential support was lacking, admittedly because Goldschmidt was of non-aryan race.

And then in the summer of 1924 von Groth retired at the age of eighty-one. This brilliant geologist and mineralogist had always declared that only one man could succeed him, namely, Victor M. Goldschmidt of Oslo. But this outstanding scholar was not appointed, again because he was of non-aryan race.

Willstätter saw that his colleagues had made his position untenable and he tendered his irrevocable resignation on June 24th, 1924.

A few days later the surgeon Sauerbruch, who had attended Margarete in a serious attack of pneumonia and had become one of Willstätter's closest friends, came to his home in the evening, drank a bottle of wine, and prepared to leave at 9 o'clock, which was unusual. To Willstätter's surprise he was asked to accompany his friend who took him to the newly built large lecture theatre of the Institute. There he was met by over three hundred of his students who presented him with a moving address assuring him of their confidence, admiration, and loyalty.

His senior colleagues also sent him a letter expressing their great appreciation of his services to science and the University and begging him to reconsider his decision.

But irrevocable that decision remained, and he only stayed long enough to aid his students to complete their researches and to make the installation of Heinrich Wieland, his successor, as smooth as possible. Then came a spate of attractive offers, a new Research Institute to be built to his own specification, head of the National Research Foundation for Physics and Chemistry in Spain, chairs at Heidelberg, Leipzig, and three American Universities. He was also offered the Directorship of research in the Siemens Company, and in 1926 his old position in the Institute at Berlin-Dahlem. All were declined. He left his laboratory and residence in September 1925 and never returned. Cordial relations with the University were however maintained. As a mark of special esteem the Senate and the Philosophical Faculty of the University passed a special unanimous resolution that " . . . Geheimrat Dr. Willstätter . . . shall as special concession be left in possession of the right of a full professor to take part in any academic ceremonies and in the meetings of the Philosophical Faculty, Section II." Invitations gradually diminished in frequency and after a few years he discovered that his name had been removed from the Faculty list. Work was carried on by a few loyal collaborators and especially after 1928 by Fr. M. Rohdewald with whom a number of enzyme studies were made, especially on the enzymes of leucocytes. This collaboration was largely effected over the telephone.

With K. Lobinger he discovered the true silicic acid, $Si(OH)_4$, and made several further incursions into inorganic chemistry, chiefly connected with adsorbents for enzymes.

His new house was in the Möhlstrasse and though relatively small was elegant and convenient. Especially after the marriage of his daughter to Dr. Ernst Bruch he found the need for some new interest. He had hitherto cultivated few hobbies and now found one in art, making a small but interesting collection. He also travelled more frequently and visited Boston to deliver the Dunham lectures, as well as this country to receive honorary degrees and the Davy Medal of the Royal Society. On two occasions he stayed with the Lecturer and Lady Robinson. On the first of these he was met at the front door by their small daughter to whom he presented a handsome doll, which with inimitable grace he christened " Richard."

Often he was accompanied by Haber and one of the last occasions was to Bad Gastein. There the paper on radical chains in oxidation mechanisms was discussed but Willstätter observes that the part he contributed was somehow omitted. A citation from " Aus meinem Leben " may explain much.

" We got to Rome, but by mistake. From the Upper Engadine we went by train to Rapallo, for we wanted to pass a few days sight-seeing in Florence. Haber gave me a lecture on the symmetry of pentaerythitol according to the views of Weissenberg. Instead of changing at Livorno we stayed in the train, because of the pentaerythitol. I made an attempt to interrupt the flow of physico-chemical ideas by observing that the sea was on the wrong side of us.

" Haber, annoyed at the interruption continued his lecture on the modification of van't Hoff's rule. Again I interrupted, the sea was definitely on the wrong side. This time Haber returned to this world. With difficulty I dissuaded him from pulling the emergency cord Thus we got to Rome and our luggage to Florence."

Other travels were to Madeira, Spain, and a memorable visit to Rehovoth to partake in the dedication of the Daniel Sieff Research Institute. His visits to England were the source of genuine pleasure both to him and to us and in 1927 he delivered the Faraday Lecture of this Society.

It is a matter of history that the rise of Hitler was accompanied by unreasoning manifestations of intense anti-semitism and Willstätter's friends, more and more urgently, advised him to emigrate.

In September 1938 he made a trip to Switzerland at the invitation of Professor Stoll who had it in mind to keep him in the country. But he still hoped to accomplish more and he determined to stay in Munich in spite of sacrifices, as long as he could do this with dignity.

After his return on November 10th, the Gestapo searched his house, having orders to take him to Dachau, but one suspects, only half-heartedly, for Willstätter was in his garden at the time. He was ordered to leave the country but though this was relatively a merciful outcome, his departure was by no means easy to arrange. There were tiresome formalities and a round of humiliating experiences at banks, customs house, Devisenstelle and Devisenüberwachungstelle. He lost in the process a great amount of property and many of his treasures of art but after a pathetic attempt to cross the frontier unofficially, he eventually entered Switzerland where his good friend Stoll, who deserves for his generous care the gratitude of all chemists, made suitable arrangements. He settled in the Spring of 1939 at Muralto-Locarno in the Villa Eremitaggio in a beautiful situation.

Willstätter's influence on the development of chemistry has been comparable to that of Baeyer. The indigo research raised the study of structure and of natural products to a new level, and the isolation of the chlorophylls and the anthocyanins brought us to another and still higher level of achievement. To reach this plane it was necessary to demonstrate success in some few cases and Willstätter showed the way. The actual cases selected were of great interest in themselves but the importance of his work is not to be assessed by that interest alone. In addition to the long record of publications, Willstätter lives in the work of his students and disciples. Among the former many names have been mentioned. Probably the first Englishman to work with him was Dr. R. Lessing who has kindly told the Lecturer that on a summer evening in 1902 Willstätter asked him to take a walk. The tropine work was nearly finished and conversation turned on the subject to which he should next devote himself. He envied Baeyer his opportunities with indigo and wondered if he could find something analogous. He said he had thought of digitalis, but this had been nibbled at and offered only a limited field. He rather fancied an attack on chlorophyll, not merely because it was of chemical interest, but also because it was vitally concerned in the processes of Nature.

This he eventually decided upon and Dr. Lessing assisted him in the very preliminary experiments with green leaves and nettles.

At a much later stage another Englishman, Dr. H. J. Page, assisted him in the study of the pigments of algae. Dr. Page became Director of the Jealotts Hill Research Station of Imperial Chemical Industries Limited and later the Director of the Imperial Institute of Tropical Agriculture, Trinidad.

Willstätter was like his father a handsome man, short in stature, but extremely dignified in bearing, yet without a trace of affectation. He was perfectly well aware of his own merits, which he had a habit of disparaging while overpraising others. His life and his scientific work speak for themselves of his sterling qualities, his power, and the inspiration he communicated to others.

At an evening reception in the Whitworth Hall, Manchester University, following a ceremony at which he was awarded an Honorary Doctorate, Willstätter moved towards a group consisting of Professor and Mrs. Bragg and Professor and Mrs. Robinson. He looked at them quizzically. Why should a young lady marry a Professor? If he is a good Professor he will neglect you and if he is no good. . . . But Dr. Willstätter whom should she choose? Just then the Chancellor, the late Earl Crawford of Balcarres passed by, and indicating him, the answer came at once—an Earl of course ! Lord Crawford was every inch a nobleman in appearance, as well as in fact. No more fitting summary of Willstätter could be given than that he also looked what he was, namely, a great gentleman in every good sense of the word.

Willstätter received many honours, some of which have already been mentioned. He was elected an Honorary Fellow of the Chemical Society in 1927 and a Foreign Member of the Royal Society in 1928. He received the Willard Gibbs medal in 1933, and was a corresponding or foreign member of many National Academies of Science, the first to so recognise him having been the Academy at Turin.

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