First Pedler Lecture.

DELIVERED ON MAY 30TH, 1929.

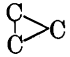
By WILLIAM HENRY PERKIN, Sc.D., LL.D., F.R.S.

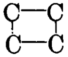
The Early History of the Synthesis of Closed Carbon Chains.

WHEN I was asked to deliver the first Pedler Lecture I was disinclined to accept the honour because it was clear to me that I could only speak with any authority on some branch of Organic Chemistry with which I had been closely associated and I saw at once that it would be very difficult to select from this field a subject which could be dealt with adequately and in an interesting manner in the course of a single lecture. During recent years, my own researches have been mainly concerned with the determination of the structure and the subsequent synthesis of alkaloids belonging to the berberine, cryptopine group and although, after I had accepted the invitation, I made more than one attempt to see whether it might be possible to sketch in a quite general way the methods which are now available for the synthesis of such alkaloids, I was in the end obliged to give up the idea, mainly because I found that it was quite impracticable to hope to deal with the matter at all effectively during the time at my disposal.

I then thought of a suggestion which had often been made to me by Professor Robinson and other friends that I should take advantage of a suitable occasion to give some account of my recollection of the early history of the experiments on the Synthesis of Closed Chains and of the difficulties which were met with in the development of the work, since it appears that nothing dealing with this aspect of the subject has ever been published. I have always felt that the obvious and indeed very serious objection to my giving a lecture of this kind is that it means talking a good deal about myself and necessitates a rather detailed account of the origin and development of much of my own experimental work. However, on looking through some of the lectures which have been delivered before the Society and are printed in the Journal, I was rather relieved to find that others who had evidently experienced the same difficulty had not hesitated to discuss, in some cases in considerable detail, their own views and experiments when the subject matter of the lecture seemed to necessitate such a course. With this encouragement and after talking the matter over with several of my colleagues, I decided to waive the objections I have to the introduction of so much matter of a personal kind and I propose, with your permission, to give you a brief account of what happened in those early days and of the train of thought which led to the inception and gradual development of the researches on the synthesis of closed carbon chains. It will be necessary that I should confine myself strictly to the early history of the subject and I must not attempt to say anything about the vast developments which have taken place since those early days and especially during recent years.

For many of us, most of all perhaps for the younger generation of chemists, it must be very difficult to appreciate the fact that, not so many years ago—certainly not more than 50 years ago—the idea was firmly fixed in the minds of chemists that Organic Chemistry must be sharply divided into two sections, namely, the Fatty Series, comprising open chains like hexane, $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_3$, and their derivatives, and the Aromatic Series, consisting of the 6-carbon ring benzene and its derivatives. It was thought to be so out of the question that intermediate carbon rings containing 3, 4, or 5 atoms





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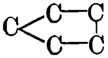


could be capable of existence that no one seems to have given them serious attention or to have attempted to construct them. Thus we find Victor Meyer in 1876 writing an interesting paper in the *Annalen* (**180**, 192) in the course of which he emphasises the fact that interactions which might conceivably have led to the formation of the 3-carbon ring had invariably resulted in the production of the isomeric unsaturated open-chain substances. It is quite clear from this paper that Victor Meyer was, in those days, firmly persuaded that the 3-carbon ring is incapable of formation and that he also held the opinion that there was no evidence to warrant the supposition that other rings smaller than six are ever likely to be obtained.

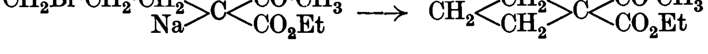
Shortly after going to Germany in 1880, I happened to translate this paper, largely for the sake of practice in German, and was much impressed by the interesting way the subject was presented and by the arguments and views brought forward by Victor Meyer. After studying for two years in Würzburg under Wislicenus, I went to Munich to continue research under Baeyer and was set the task of attempting to make benzoylacetic ester. This substance was ultimately prepared, as you all know, by making use of a method which arose out of his indigo work and was suggested to me by Baeyer, namely, by treating phenylpropiolic ester with sulphuric acid and pouring the mixture on ice, and I shall presently show that this research had some bearing on the subsequent work on ring formation. Soon after I had started work in Munich, I think it was in November 1882, Victor Meyer paid one of his frequent visits to Baeyer's laboratory and I then ventured to remind him of his paper in the *Annalen* and to ask him whether he was still of the same opinion or whether he had altered or modified his views. He was kind enough to ask me to supper and to spend the rest of the evening at the Hofbräuhaus with him and I remember the occasion as if it had occurred only yesterday. It was of course a great opportunity and privilege for so young a student as I then was to be invited to spend the evening and talk chemistry with a man of such eminence. During and after the simple meal he discussed the matter of ring formation in great detail and with his usual nervous energy, emphasising in particular the absence of any evidence of the existence of rings made up of 3, 4, or 5 carbon atoms, and when I told him that it was my intention to attempt to prepare substances containing such rings, he said he was much impressed by my enthusiasm but thought I should be well advised at so early a stage in my career to work at something more promising and more likely to give positive results.

Victor Meyer's main argument, to which he returned over and over again, was this, that if rings smaller than 6 are capable of formation and are stable enough to exist, how was it that nothing was known about them? He pointed to the large amount of synthetical work which had already been done in so many directions and emphasised the fact that while such synthetical work had not infrequently led to the formation of derivatives of benzene, as, for example, in the case of the conversion of acetone into mesitylene, no such condensations had so far been met with which had resulted in the formation of rings containing less than 6 carbon atoms. Next morning, I told Baeyer about the conversation I had had the previous evening with Victor Meyer and it was quite clear that he also held the same views and was in general agreement with the arguments which Victor Meyer had brought forward. He saw no reason why we should assume that rings containing a smaller or larger number of carbon atoms than six are capable of existence; on the contrary, all experience was against such an assumption. If substances derived from such rings are possible and have reasonable stability, how was it, I particularly remember his saying, that they had never been met with in Nature?

However, I am quite sure that Baeyer, even at that time, was not completely satisfied with the position he had taken up, because soon afterwards and on more than one occasion he asked me if I was still interested in the possible existence of the smaller rings and made some encouraging remarks when I told him I was hoping to start work on them in a short time. Moreover he evidently discussed the matter with Emil Fischer, because on one of the occasions when Emil Fischer visited the Munich laboratories and had been talking to me about the work on benzoylacetic ester and especially about the isolation of dibenzoylmethane, in which he was particularly interested, he told me as he was leaving that Baeyer had spoken to him about my wish to start synthetical work on the formation of derivatives of the smaller carbon rings. He thought it unlikely that I should succeed in obtaining such substances and said that even if they were formed in small quantity they would probably exhibit little stability and it would be very difficult to demonstrate their existence sufficiently conclusively to convince the chemical world.

The investigation of benzoylacetic ester, on which I was engaged at that time, proved to be tedious and often very disappointing, partly on account of the difficulty associated with the preparation of the crude ester in any quantity, but mainly because the method of fractional distillation under low pressure had not then been developed and consequently it was almost impossible to obtain any of the oily substitution derivatives in a state even of approximate purity.

The plan I adopted was to carry out each new experiment in the first place with acetoacetic ester and then to apply the experience I had obtained to the case of benzoylacetic ester. In the course of the preparation of dipropylacetoacetic ester, I had made a quantity of the monopropyl derivative, $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}CO{\cdot}CH_3$, from propyl bromide by the usual process : and was proposing to introduce the second propyl group in a similar manner when it occurred to me that, if this mono-substitution derivative could be brominated at the end of the chain, the sodium derivative of the product might decompose with elimination of sodium bromide and formation of acetyltetramethylenecarboxylic ester containing the 4-carbon ring :

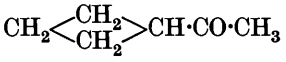


$$\mathrm{CH_2Br{\cdot}CH_2{\cdot}}\begin{matrix}\mathrm{CH_2}\\ \mathrm{Na}\end{matrix}\!>\mathrm{C}<\!\begin{matrix}\mathrm{CO{\cdot}CH_3}\\ \mathrm{CO_2Et}\end{matrix} \longrightarrow \mathrm{CH_2}<\!\begin{matrix}\mathrm{CH_2}\\ \mathrm{CH_2}\end{matrix}\!>\mathrm{C}<\!\begin{matrix}\mathrm{CO{\cdot}CH_3}\\ \mathrm{CO_2Et}\end{matrix}$$

As there was clearly no prospect of discovering a process for introducing the bromine atom into the end position in the propyl group of propylacetoacetic ester, the only alternative seemed to be to start with a dibromide containing the two bromine atoms in the required positions, that is to say, to start with trimethylene bromide, $CH_2Br{\cdot}CH_2{\cdot}CH_2Br$. Then the ring formation might take place in the way I have just indicated.

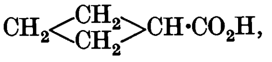
It happened that at that time I had in my possession small quantities of ethylene bromide, propylene bromide and trimethylene bromide as well as of other bromides and iodides which had been prepared with quite a different object in view, namely, that of determining the relative stability of the halogen atoms on heating with water, dilute alkalis, etc. I had already made preliminary experiments on these lines which seemed to promise interesting results, but the research was never developed. With my small supply of trimethylene bromide, I carried out the condensation with the sodium derivative of acetoacetic ester and obtained to my surprise and delight a small quantity of an ester which, on analysis, gave numbers agreeing with those required for acetyltetramethylenecarboxylic ester.

Since this substance is a disubstituted acetoacetic ester, I expected that hydrolysis with alkali would lead to the formation of acetyltetramethylene and tetramethylenecarboxylic acid,



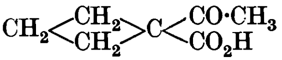
$$CH_2<\begin{matrix}CH_2\\CH_2\end{matrix}>CH\cdot CO\cdot CH_3$$

and



$$CH_2<\begin{matrix}CH_2\\CH_2\end{matrix}>CH\cdot CO_2H,$$

but the sole product of hydrolysis was a beautifully crystalline acid which gave analytical values agreeing closely with those calculated for acetyltetramethylenecarboxylic acid,



$$CH_2<\begin{matrix}CH_2\\CH_2\end{matrix}>C<\begin{matrix}CO\cdot CH_3\\CO_2H\end{matrix}$$

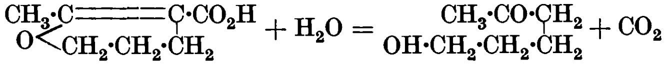
so that decomposition with elimination of carbon dioxide or the acetyl group, so characteristic of substituted acetoacetic esters, had not occurred in this case. When I told Baeyer of these results and showed him the analyses and the specimens, he thought the matter so important that he decided to communicate the results to the Bavarian Academy that same day (31st January, 1883) and not to wait for the next number of the *Berichte*, in case, as he said, someone else might be engaged in a similar series of experiments. So the paper was written forthwith in his study and Baeyer took it at once to the Academy and it was also at the same time sent to the *Berichte*, in which it appeared under the heading " Einwirkung von Trimethylenbromid auf Natracetessigäther " in the next number (p. 208).

Victor Meyer not only wrote me a charming letter but when he visited Baeyer shortly afterwards he told him how greatly interested he was in the results. No suspicion was entertained at that time that the experimental results recorded in the paper had been incorrectly interpreted, but three years later I found, quite accidentally, that the decomposition had in fact taken quite a different course from that described and it became gradually evident that no 4-carbon ring is produced as the result of the interaction of trimethylene bromide with the sodium derivative of acetoacetic ester. During the recrystallisation of an unusually large quantity of the so-called acetyltetramethylenecarboxylic acid from boiling water, it was noticed that carbon dioxide was gradually given off and, after boiling had been continued until the evolution had ceased, no acid separated on cooling. It was expected that the solution would now be found to contain acetyltetramethylene, but in place of this a substance was isolated which on careful investigation proved to be acetobutyl alcohol, $CH_3\cdot CO\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot OH$.

There was just a possibility that this ketone alcohol might have been formed from acetyltetramethylene by the addition of water and disruption of the 4-carbon ring, but it gradually became evident that it was the interpretation of the course of the interaction of trimethylene bromide with the sodium derivative of acetoacetic ester which was at fault. It is now known that the following scheme represents what actually takes place. The bromopropylacetoacetic ester produced in the first stage yields, on treatment with sodium ethylate, the sodium derivative of the tautomeric modification, and this decomposes on heating with the formation of methyldehydrohexonecarboxylic ester :

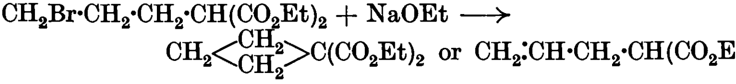
$$\begin{array}{l}CH_3\cdot C(ONa){=}C\cdot CO_2Et\\ \quad BrCH_2\cdot CH_2\cdot CH_2\end{array} \longrightarrow \begin{array}{l}CH_3\cdot C{=\!=\!=\!=}C\cdot CO_2Et\\ \quad O{<}CH_2\cdot CH_2\cdot CH_2\end{array}$$

The free acid, which was thought to be acetyltetramethylenecarboxylic acid, is therefore methyldehydrohexonecarboxylic acid, or in other words it is the carboxylic acid of the anhydride of acetobutyl alcohol and as such it decomposes on boiling with water into acetobutyl alcohol and carbon dioxide :



$$\begin{array}{l}CH_3\cdot C{=\!=\!=\!=}C\cdot CO_2H\\ \quad O{<}CH_2\cdot CH_2\cdot CH_2\end{array} + H_2O = \begin{array}{r}CH_3\cdot CO\cdot CH_2\\ OH\cdot CH_2\cdot CH_2\cdot CH_2\end{array} + CO_2$$

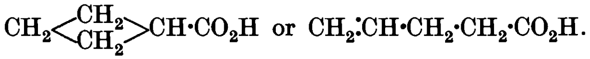
In complete ignorance of the incorrect interpretation of the initial synthesis, the new method was vigorously developed in various directions and in July of 1883 a paper was published in the *Berichte* (p. 1787) containing a description of the action of trimethylene bromide on the sodium derivative of malonic ester. It was recognised that the decomposition might proceed in two directions with the formation either of tetramethylenedicarboxylic ester or of allylmalonic ester,



$$CH_2Br\cdot CH_2\cdot CH_2\cdot CH(CO_2Et)_2 + NaOEt \longrightarrow$$

$$CH_2{<}\begin{array}{c}CH_2\\ CH_2\end{array}{>}C(CO_2Et)_2 \text{ or } CH_2{:}CH\cdot CH_2\cdot CH(CO_2Et)_2,$$

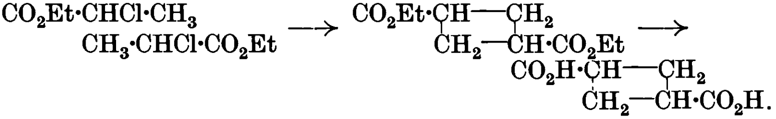
and the acid obtained on hydrolysis and elimination of carbon dioxide might be either tetramethylenecarboxylic acid or allylacetic acid,



$$CH_2{<}\begin{smallmatrix}CH_2\\CH_2\end{smallmatrix}{>}CH\cdot CO_2H \text{ or } CH_2{:}CH\cdot CH_2\cdot CH_2\cdot CO_2H.$$

Careful examination showed that the acid produced in this way was not allylacetic acid: it distilled at 193°, whereas allylacetic acid distils at 185°, and it did not, like the latter, combine with bromine or hydrobromic acid. Also the melting points and boiling points of a number of its derivatives were found to differ widely from those of the corresponding derivatives of allylacetic acid. The subsequent exhaustive examination of the acid, including the determination of the magnetic rotation, refractive index and other physical properties, entirely confirmed the view that it is tetramethylenecarboxylic acid and this view has indeed never been disputed.

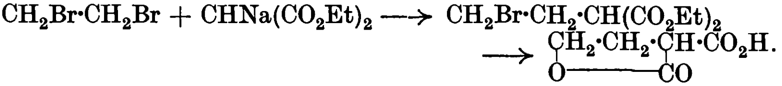
This acid is, however, not the first derivative of tetramethylene to be synthesised, because in 1881 (*Annalen*, **208**, 334) Markownikoff and Krestownikoff obtained an acid, m. p. 171°, which they named tetrylenedicarboxylic acid, by the hydrolysis of the ester which is formed in small quantity when ethyl α-chloropropionate is heated with dry sodium ethylate:



$$\begin{array}{l}CO_2Et\cdot CHCl\cdot CH_3\\ \quad CH_3\cdot CHCl\cdot CO_2Et\end{array} \longrightarrow \begin{array}{l}CO_2Et\cdot CH—CH_2\\ \qquad\quad CH_2—CH\cdot CO_2Et\end{array} \longrightarrow \begin{array}{l}CO_2H\cdot CH—CH_2\\ \qquad\quad CH_2—CH\cdot CO_2H.\end{array}$$

This acid was subsequently investigated by E. Haworth and myself (J., 1898, **73**, 330) and found to exist in *cis*- and *trans*-modifications melting at 133° and 171° and there can be no doubt that the acid obtained by the Russian chemists was, in fact, *trans*-tetramethylene-1 : 3-dicarboxylic acid and was the first derivative of tetramethylene to be described. It is remarkable that this observation should have called forth so little comment and that this curious decomposition was not extended to many other cases.

During the course of the experiments on the action of trimethylene bromide on the sodium derivatives of acetoacetic ester and malonic ester, a parallel series of experiments was started using, in the place of trimethylene bromide, the more readily accessible ethylene bromide and a statement to this effect was made at the end of the first paper, published in 1883, to which I have already referred. This statement brought me into conflict with Fittig, because Fittig and his pupil Roeder happened also to be working at the action of ethylene bromide on the sodium derivative of malonic ester with an object entirely different from that which prompted my experiments. Fittig and his pupils were at that time actively engaged in the investigation of the conditions of formation and properties of lactones, a series of researches of great importance which will always be associated with the name of Fittig and with the Strassburg laboratories in which the work was carried out. It was in connexion with these lactone researches, and because I had said that I was engaged in similar work, that a short note by Fittig and Roeder appeared in the *Berichte* of 1883 (p. 372), giving a brief outline of their experiments on the action of ethylene bromide on the sodium derivative of malonic ester. They state that their expectation was that the interaction would proceed with the formation of bromoethylmalonic ester and that this, on hydrolysis, would yield butyrolactone carboxylic acid :

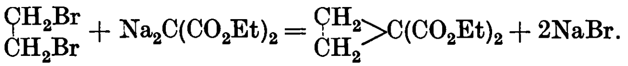


$$\mathrm{CH_2Br{\cdot}CH_2Br + CHNa(CO_2Et)_2 \longrightarrow CH_2Br{\cdot}CH_2{\cdot}CH(CO_2Et)_2}$$
$$\longrightarrow \begin{array}{l}\mathrm{CH_2{\cdot}CH_2{\cdot}CH{\cdot}CO_2H.}\\ \mathrm{O\text{————}CO}\end{array}$$

But instead of butyrolactone carboxylic acid they obtained a dibasic acid, m. p. 140°, which they considered was vinylmalonic acid and which they subsequently named vinaconic acid. The formation of the vinyl acid was easily explained by assuming that the bromoethylmalonic ester, first formed, lost hydrobromic acid during the treatment with sodium ethylate and subsequent hydrolysis with alcoholic potash :

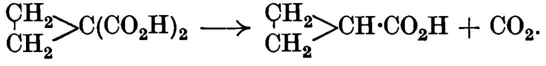
$$\mathrm{CH_2Br{\cdot}CH_2{\cdot}CH(CO_2Et)_2 \longrightarrow CH_2{:}CH{\cdot}CH(CO_2H)_2}$$

In a paper published in the *Berichte* (p. 54) in January, 1884, I described the results of my own experiments on the action of ethylene bromide on the sodium derivative of malonic ester and interpreted the course of the change in a manner different from that suggested by Fittig. In my view the product of the interaction was trimethylenedicarboxylic ester produced according to the scheme :



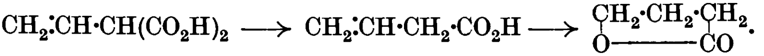
$$\begin{array}{l}\mathrm{CH_2Br}\\ \mathrm{CH_2Br}\end{array} + \mathrm{Na_2C(CO_2Et)_2} = \left.\begin{array}{l}\mathrm{CH_2}\\ \mathrm{CH_2}\end{array}\right> \mathrm{C(CO_2Et)_2 + 2NaBr.}$$

On hydrolysing the ester, I obtained an acid of m. p. 140° which careful comparison showed was identical with the vinaconic acid of Fittig and Roeder, but, instead of representing this as vinylmalonic acid, I, for various reasons some of which were not published at that time, formulated this acid as trimethylenedicarboxylic acid. When this acid was heated at 210° it decomposed with loss of carbon dioxide and formation of a monobasic acid distilling at 181°, which I named trimethylenecarboxylic acid :



$$\left.\begin{array}{l}\mathrm{CH_2}\\ \mathrm{CH_2}\end{array}\right> \mathrm{C(CO_2H)_2} \longrightarrow \left.\begin{array}{l}\mathrm{CH_2}\\ \mathrm{CH_2}\end{array}\right> \mathrm{CH{\cdot}CO_2H + CO_2.}$$

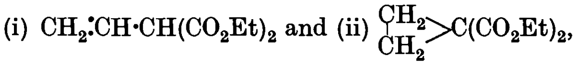
Fittig and Roeder did not publish the detailed account of their experiments until a year later (*Annalen*, 1885, **227**, 13) and in this paper Fittig discussed my view at great length and accused me, perhaps not unjustly, of not having brought forward a single argument in support of my representation of these substances as derivatives of the 3-carbon ring, trimethylene. It must be conceded that, at that time, the balance of the published evidence was in favour of the view of Fittig that the acid of m. p. 140° is vinylmalonic acid. Fittig found that, on heating, it yields along with the monobasic acid—vinylacetic acid according to his view—a not inconsiderable quantity of butyrolactone and thus the monobasic acid exhibits the well-known property of $\beta\gamma$-unsaturated acids of passing into γ-lactones on distillation :



$$CH_2{:}CH\cdot CH(CO_2H)_2 \longrightarrow CH_2{:}CH\cdot CH_2\cdot CO_2H \longrightarrow \begin{array}{l}CH_2\cdot CH_2\cdot CH_2\\ O\text{————}CO\end{array}.$$

The dibasic acid also combines with hydrobromic acid with great ease to yield γ-bromoethylmalonic acid, and this behaviour may again be said to be in favour of the unsaturated vinylmalonic acid formula.

Arguing from analogy, the unsaturated vinylmalonic acid should also combine readily with bromine to yield $\beta\gamma$-dibromoethylmalonic acid, but this was found not to be the case. Fittig himself expressed his surprise that not only does the dibasic acid not react with bromine but, what is still more remarkable, the solution of the monobasic acid in chloroform may be left in contact with bromine for days without any visible decolorisation. This is a very different behaviour from that exhibited by allylmalonic acid or by the crotonic acids, all of which rapidly decolorise bromine. As you may imagine, the determination of the constitution of these acids proved, in those days, to be a very difficult matter and it was particularly unfortunate that the bromine atom in vinyl bromide, $CH_2{:}CHBr$, is so tightly bound that this substance will not react with the sodium derivative of malonic ester, otherwise this synthesis of vinylmalonic ester would clearly have settled the matter once for all. To cut a long story short, I may say that the proof that these acids are not unsaturated but are derivatives of the 3-carbon ring trimethylene was subsequently obtained in the following manner. If the two suggested formulæ for the product of the action of ethylene bromide on the sodium derivative of malonic ester, namely,



$$\text{(i) } CH_2{:}CH\cdot CH(CO_2Et)_2 \text{ and (ii) } \begin{array}{l}CH_2\\ CH_2\end{array}\!\!>C(CO_2Et)_2,$$

are examined it will be recognised that the former is a monosubstitution derivative, whereas the latter is a disubstitution derivative, of malonic ester: the former may be compared with ethylmalonic ester and the latter with dimethylmalonic ester. The ester (i) still has a hydrogen atom replaceable by sodium and should therefore react with sodium ethylate and benzyl chloride to yield benzylvinylmalonic ester, $CH_2{:}CH{\cdot}C(C_7H_7)(CO_2Et)_2$, whereas the ester (ii) does not contain a hydrogen atom replaceable by sodium and cannot therefore yield a benzyl substitution derivative. When the experiment was made, it was found that, not only was no benzyl derivative produced, but that almost the whole of the original ester was recovered unchanged. This behaviour is clearly strong evidence in favour of the constitution (ii).

Just at that time an important piece of work was carried out by the Belgian chemist, Franchimont, who showed that monosubstituted malonic acids react with nitric acid in the cold with loss of two molecules of carbon dioxide, whereas disubstituted malonic acids are unchanged by this treatment. Professor Franchimont was good enough to try this interesting experiment with some of the dibasic acid, m. p. 140°, which I sent him and he reported that it did not react with nitric acid and therefore behaved as a disubstituted malonic acid. A very pure specimen of the ethyl ester of the acid of m. p. 140° was then prepared from the silver salt by the action of ethyl iodide and its magnetic rotation and refractive index were determined; the values obtained showed very clearly that the ester and therefore the acid could not be unsaturated.

Ultimately, in 1899, vinylacetic acid was prepared by J. Wislicenus (*Ber.*, **32**, 2047) and by Fichter and Krafft (*ibid.*, p. 2799) from β-hydroxyglutaric acid by distillation,

$$CO_2H{\cdot}CH_2{\cdot}CH(OH){\cdot}CH_2{\cdot}CO_2H \longrightarrow CH_2{:}CH{\cdot}CH_2{\cdot}CO_2H + CO_2 + H_2O,$$

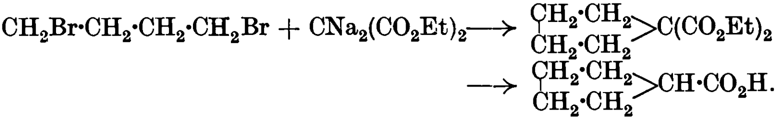
and in 1903 by Houben (*Ber.*, **36**, 2897) from the magnesium derivative of allyl bromide by decomposition with carbon dioxide:

$$CH_2{:}CH{\cdot}CH_2{\cdot}MgBr \longrightarrow CH_2{:}CH{\cdot}CH_2{\cdot}CO_2H$$

The acid obtained by either process distils at 168° and combines immediately with bromine; it therefore has properties quite different from those of the acid obtained by Fittig and by myself by heating the acid of m. p. 140°, since this distils at 181° and is so remarkably stable to bromine. It is clear, therefore, that the synthesis of vinylacetic acid supplies the final proof that the acid, b. p. 181°, must be regarded as trimethylenecarboxylic acid, and that the acid, m. p. 140°, is trimethylenedicarboxylic acid.

Although the synthesis of trimethylenecarboxylic acid in 1883 was the first occasion on which a derivative of trimethylene had been obtained in a pure state, it cannot be described as the first synthesis of the 3-carbon ring, because Freund, in 1882 (*Monatsh.*, **3**, 625), had treated trimethylene bromide with sodium and obtained a gas which was subsequently shown to contain trimethylene mixed with much propane and propylene. In 1887, Gustavson (*J. pr. Chem.*, [2], **36**, 300) greatly improved the method of preparation by substituting zinc and alcohol for sodium, but the gas was again contaminated with propane and probably with hydrogen. Lastly, in 1907, Willstätter (*Ber.*, **40**, 4459), employing also the action of zinc on an alcoholic solution of trimethylene bromide, but greatly improving the conditions and then liquefying the gas, succeeded in isolating trimethylene in a pure state. Trimethylene boils at about —35° and when heated, especially in contact with a catalyst such as alumina, readily undergoes isomerisation into propylene.

The interval between the Fatty and the Aromatic Series had now been considerably lessened by the synthesis and examination of the trimethylene- and tetramethylene-carboxylic acids and the next step was to devise some method for the preparation of a derivative of the 5-carbon ring. There seemed every reason to believe that pentamethylenecarboxylic acid might be readily obtained by making use of the method which had been so successful in the previous cases, namely, by acting on the sodium derivative of malonic ester with tetramethylene bromide :



$$CH_2Br{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Br + CNa_2(CO_2Et)_2 \longrightarrow \begin{matrix}CH_2{\cdot}CH_2\\ |\\ CH_2{\cdot}CH_2\end{matrix}\!>C(CO_2Et)_2 \longrightarrow \begin{matrix}CH_2{\cdot}CH_2\\ |\\ CH_2{\cdot}CH_2\end{matrix}\!>CH{\cdot}CO_2H.$$

Unfortunately, at that time tetramethylene bromide was unknown and it was not until 1894 or 10 years later (J., 1894, **65**, 86) that it was obtained accidentally by a process which for a long time was not understood. The attempt was being made to convert trimethylene bromide into the dicyanide, then into pentamethylenediamine by reduction, then into the glycol by nitrous acid, and then into pentamethylene bromide by treatment with hydrobromic acid,

$$CH_2Br{\cdot}CH_2{\cdot}CH_2Br \qquad CN{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$$

$$NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$$

$$OH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH \qquad CH_2Br{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Br,$$

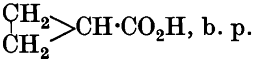
with the object of using the dibromide for the synthesis of hexamethylenecarboxylic acid by the usual method. But the substance actually obtained as the result of this series of changes was found to be a mixture of pentamethylene bromide with a good deal of a lower-boiling bromide and, on very careful fractionation, this proved to be tetramethylene bromide, one CH_2-group having in some way been lost during its formation. The solution of the mystery may be taken to be the following: The strongly alkaline potassium cyanide which was in common use in those days, evidently acted as if it were a mixture of cyanide and hydroxide and led to the formation of a good deal of hydroxy-propyl cyanide. When this was reduced and then treated with nitrous acid and then with hydrobromic acid, tetramethylene bromide, the substance for which we had so long searched in vain, was produced :

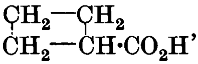
$$CH_2Br\cdot CH_2\cdot CH_2Br \qquad OH\cdot CH_2\cdot CH_2\cdot CH_2\cdot CN$$

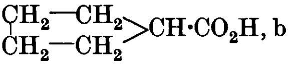
$$OH\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot NH_2$$

$$OH\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot OH \qquad CH_2Br\cdot CH_2\cdot CH_2\cdot CH_2Br$$

When the sodium derivative of malonic ester was digested with this new dibromide, pentamethylenedicarboxylic ester was produced in almost quantitative yield, and this, on hydrolysis and elimination of carbon dioxide, supplied the long-sought-for pentamethylenecarboxylic acid, a substance characterised by great stability. Thus the gap between the fatty and the aromatic series had now been bridged by the synthesis of the following acids :

Trimethylenecarboxylic acid,  $\begin{matrix}CH_2\\ |\\ CH_2\end{matrix}\!\!>CH\cdot CO_2H$, b. p. 181°.

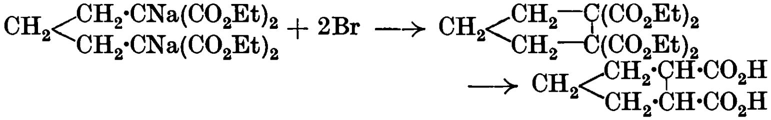
Tetramethylenecarboxylic acid,  $\begin{matrix}CH_2-CH_2\\ |\quad\;\;\; |\\ CH_2-CH\cdot CO_2H\end{matrix}$, b. p. 195°.

Pentamethylenecarboxylic acid,  $\begin{matrix}CH_2-CH_2\\ |\\ CH_2-CH_2\end{matrix}\!\!>CH\cdot CO_2H$, b. p. 215°.

Finally the pentamethylene bromide, obtained in the way I have just described, was purified by careful fractionation and caused to interact with the sodium derivative of malonic ester, and this led to the synthesis of hexamethylenecarboxylic acid (b. p. 232°), which proved to be identical with the hexahydrobenzoic acid resulting from the reduction of benzoic acid.

I have already mentioned that the synthesis of pentamethylenecarboxylic acid had to be postponed over and over again because of the impossibility of obtaining tetramethylene bromide and that the acid was actually not prepared until 1894. In view of this difficulty, another method had to be devised for the synthesis of the 5-carbon ring, and this ring was produced for the first time in 1885 or nearly 10 years before the date of the synthesis of pentamethylenecarboxylic acid. It had been noticed from the first that when ethylene bromide or trimethylene bromide interacts with the sodium derivative of malonic ester, there are always formed, along with the trimethylene- or tetramethylene-dicarboxylic esters, small quantities of highboiling substances, and these were found to be derived from two molecules of malonic ester. Thus, in the cases just mentioned, these secondary products are butanetetracarboxylic ester and pentanetetracarboxylic ester, $(CO_2Et)_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Et)_2$ and $(CO_2Et)_2CH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Et)_2$. On account of the fact that these substances readily yield disodium derivatives, they have proved to be of considerable value for ordinary synthetical purposes. But of much more interest is the fact that they serve as valuable and convenient starting points for the synthesis of closed-chain derivatives, and their use has made possible, as I will presently show, the preparation of a great variety of interesting and important substances which could hardly have been obtained by any other method.

Pentanetetracarboxylic ester was the starting point in the first synthesis of the pentamethylene ring, a synthesis which was carried out in the autumn of 1885 and published in December of that year (*Ber.*, **18**, 3246). When the disodium derivative of this ester was treated with bromine, ring closure occurred, and the pentamethylenetetracarboxylic ester obtained, in almost quantitative amount, yielded on hydrolysis and elimination of carbon dioxide pentamethylene-1 : 2-dicarboxylic acid,



$$CH_2\Big\langle\begin{array}{l}CH_2{\cdot}CNa(CO_2Et)_2\\ CH_2{\cdot}CNa(CO_2Et)_2\end{array} + 2Br \longrightarrow CH_2\Big\langle\begin{array}{l}CH_2-C(CO_2Et)_2\\ CH_2-C(CO_2Et)_2\end{array}$$

$$\longrightarrow CH_2\Big\langle\begin{array}{l}CH_2{\cdot}CH{\cdot}CO_2H\\ CH_2{\cdot}CH{\cdot}CO_2H\end{array}$$

an acid which was later shown to exist in well-defined *cis*- and *trans*-modifications. This was the first synthesis of the 5-carbon ring.

The fact that the formation of the 5-carbon ring takes place so readily and that the pentamethylenedicarboxylic acid obtained in this way should prove to be a substance of such marked, it might even be said unusual, stability excited a great deal of interest at the time.

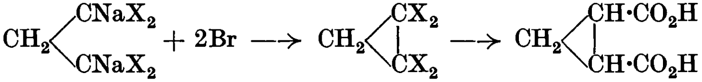
During 1885, Baeyer was gradually working out his "Spannungs Theorie," a conception which was destined to exert so profound an influence on the whole subject of ring closure. I remember that on two occasions he invited me into his study and explained to me, with the aid of models which had been specially made, his views on the stability and ease of formation of rings based on the tetrahedral configuration of the carbon atom, and these views gradually gave rise to the "Spannungs Theorie." This remarkable theory, published in August, 1885 (*Ber.*, **18**, 2278), occupies only two pages of print and its description always seems to me to be a striking example of how much can be said in a very small space.

As is well known, one of the consequences of the theory is that the 5-carbon ring should prove to be the most stable and most easily formed of all rings or, as Baeyer himself puts it, " pentamethylene should be the most stable configuration and should be formed rather more easily than hexamethylene."

In discussing this point with me, Baeyer remarked that it was unfortunate that no pentamethylene derivative had so far been prepared so as to make the direct comparison possible. It is therefore not difficult to picture how greatly interested Baeyer was when a short time after the publication of his theory the synthesis of pentamethylene-1 : 2-dicarboxylic acid, which I have just described, actually demonstrated not only that the 5-carbon ring is produced with great ease but that it is also characterised by great stability. He considered that this synthesis confirmed in a very welcome manner the views which he had so shortly before developed in his " Spannungs Theorie."

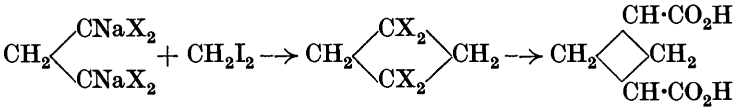
The method which had been used so successfully in the synthesis of the pentamethylene ring was now developed in a great many directions and it was found that substances of the type $(CO_2Et)_2CH\cdot[CH_2]_n\cdot CH(CO_2Et)_2$ lend themselves so readily to so great a variety of ring syntheses that they may perhaps be said to be the most valuable reagents we possess for this purpose. Although much of the synthetical work carried out with the aid of substances of this kind dates from before 1894 and may thus claim to be included in an account of the Early History of Ring Closure, it would take me far too long to go into this matter in any detail. I venture, however, to introduce a short table which gives in a general way some idea of the scope of these synthetical methods and includes one or two of the more interesting special cases (X = CO_2Et).

(i)



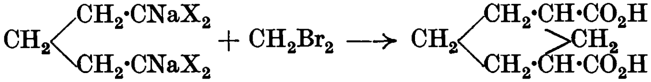
Trimethylene-1 : 2-dicarboxylic acid.

(ii)



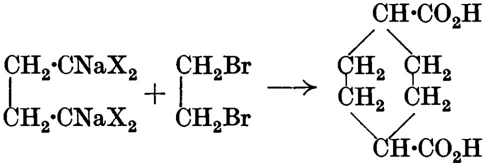
Tetramethylene-1 : 3-dicarboxylic acid.

(iii)



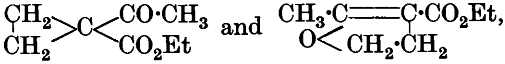
Hexahydro*iso*phthalic acid.

(iv)



Hexahydroterephthalic acid.

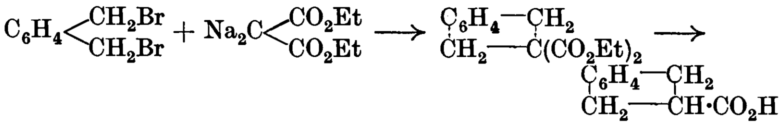
The last syntheses to which I will refer, because they are perhaps in many ways as novel and interesting as any of those I have already mentioned, are the syntheses of derivatives of hydrindonaphthene (hydrindene) and of tetrahydronaphthalene published by Baeyer conjointly with myself in the *Berichte* of January and February, 1884 (pp. 122 and 448). I pointed out earlier in this lecture that when trimethylene bromide interacts with the sodium derivative of acetoacetic ester, the process follows an unexpected course leading to the formation of methyldehydrohexonecarboxylic ester instead of acetyltetramethylenecarboxylic ester as had been expected. When, in an analogous series of experiments, commenced at the same time, the trimethylene bromide was replaced by ethylene bromide, a mixture of esters was obtained which could not at first be separated into its constituents and it was not until much later that it was possible to show that this product consists essentially of acetyltrimethylenecarboxylic ester mixed with varying quantities of methyldehydropentonecarboxylic ester,



the process in this case having taken place in the two possible directions.

The main difficulty was that it was not found possible to isolate any of the products in a crystalline condition, and it occurred to me that if I replaced, in the interaction with the sodium derivative of acetoacetic ester, the ethylene bromide by phenylethylene bromide, $C_6H_5{\cdot}CHBr{\cdot}CH_2Br$, the esters produced or more probably the corresponding acids might be crystalline and therefore lend themselves more readily to separation.

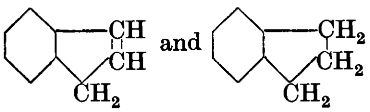
When I mentioned this idea to Baeyer, I thought that he did not at the time seem to be interested, but a few days afterwards he told me that, in thinking the matter over, a modification of the idea had suggested itself to him which he thought might lead to results of considerable interest and importance. If, he said, instead of phenylethylene bromide, the then unknown isomeric bromide, *o*-xylylene bromide, $C_6H_4(CH_2Br)_2$, could be prepared, it might react with malonic ester to yield derivatives of hydrindonaphthene (hydrindene) and he proceeded to sketch out the scheme exactly as he wrote it later for publication in the *Berichte* :



$$C_6H_4 < \begin{matrix}CH_2Br\\ CH_2Br\end{matrix} + Na_2C < \begin{matrix}CO_2Et\\ CO_2Et\end{matrix} \longrightarrow \begin{matrix}C_6H_4-CH_2\\ CH_2-C(CO_2Et)_2\end{matrix} \longrightarrow \begin{matrix}C_6H_4-CH_2\\ CH_2-CH\cdot CO_2H\end{matrix}$$

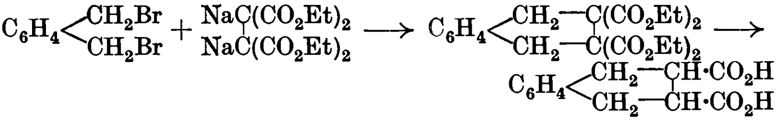
He told me that he had long wished to synthesise indene, or indonaphthene as he then called it, and examine its properties mainly because of its relationship to indole and to the whole indigo group, the investigation of which had occupied him for so many years. It was most fortunate that *o*-xylene could be obtained at that time in almost pure condition from the firm of Langenfeld and Reuter, but Baeyer was very doubtful whether, on bromination at the boiling point, this would yield *o*-xylylene bromide in anything like a pure condition. He rather expected that the product would contain considerable quantities of the isomeride, $C_6H_4(CHBr_2)\cdot CH_3$, as well as of substances containing bromine substituted in the benzene ring. A mixture is indeed formed under these conditions, but *o*-xylylene bromide has fortunately so great a facility for crystallising that there is not much difficulty in preparing it in a pure condition. The main trouble proved to be the effect of this substance on the eyes, which was much more severe than had been anticipated.

The interaction between *o*-xylylene bromide and malonic ester proceeded exactly as Baeyer had predicted and the hydrindonaphthenedicarboxylic ester so obtained yielded, on hydrolysis and elimination of carbon dioxide, hydrindonaphthenecarboxylic acid. It was shown at a later date (1894) that the barium salt of this acid is decomposed on heating with separation of indonaphthene (indene), and since this on reduction yields hydrindonaphthene (hydrindene),



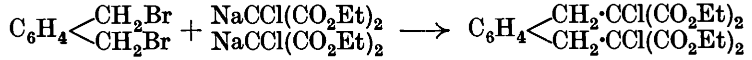
the synthesis of both these important hydrocarbons was accomplished in this way.

The next step was to extend these methods to the hexahydronaphthalene series and this was done in two different ways both of which led ultimately to the same result. In the first process *o*-xylylene bromide and the disodium derivative of acetylenetetracarboxylic ester were heated with alcohol in a sealed tube and the product was hydrolysed; an acid was then obtained which, on heating at 185°, decomposed with elimination of carbon dioxide and formation of tetrahydronaphthalenedicarboxylic acid :



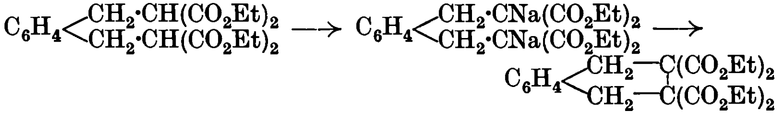
$$C_6H_4\left<\begin{array}{l}CH_2Br\\CH_2Br\end{array}\right. + \begin{array}{l}NaC(CO_2Et)_2\\NaC(CO_2Et)_2\end{array} \longrightarrow C_6H_4\left<\begin{array}{l}CH_2-C(CO_2Et)_2\\CH_2-C(CO_2Et)_2\end{array}\right. \longrightarrow C_6H_4\left<\begin{array}{l}CH_2-CH\cdot CO_2H\\CH_2-CH\cdot CO_2H\end{array}\right.$$

The still more interesting second process consisted in boiling an alcoholic solution of the sodium derivative of chloromalonic ester with xylylene bromide; rather unexpectedly, the following process then took place almost quantitatively :



$$C_6H_4\left<\begin{array}{l}CH_2Br\\CH_2Br\end{array}\right. + \begin{array}{l}NaCCl(CO_2Et)_2\\NaCCl(CO_2Et)_2\end{array} \longrightarrow C_6H_4\left<\begin{array}{l}CH_2\cdot CCl(CO_2Et)_2\\CH_2\cdot CCl(CO_2Et)_2\end{array}\right.$$

There was of course always the possibility that the sodium derivative of chloromalonic ester would interact with itself with the formation of the substance $(CO_2Et)_2C{:}C(CO_2Et)_2$, but the bromine atoms in *o*-xylylene bromide proved to be more reactive than the chlorine atom in chloromalonic ester, so that the process proceeded almost entirely in the direction I have indicated. When *o*-xylylenedichlorodimalonic ester is reduced by zinc dust, it yields *o*-xylylenedimalonic ester, the disodium derivative of which is readily acted on by iodine with closure of the ring, and the ester produced is identical with the tetrahydronaphthalenetetracarboxylic ester obtained with the aid of acetylenetetracarboxylic ester in the way I have just described.



$$C_6H_4\left<\begin{array}{l}CH_2\cdot CH(CO_2Et)_2\\CH_2\cdot CH(CO_2Et)_2\end{array}\right. \longrightarrow C_6H_4\left<\begin{array}{l}CH_2\cdot CNa(CO_2Et)_2\\CH_2\cdot CNa(CO_2Et)_2\end{array}\right. \longrightarrow C_6H_4\left<\begin{array}{l}CH_2-C(CO_2Et)_2\\CH_2-C(CO_2Et)_2\end{array}\right.$$

The last step in this investigation consisted in heating the silver salt of tetrahydronaphthalenedicarboxylic acid in a test-tube; decomposition took place readily with sublimation of naphthalene. This process constitutes one of the best-known syntheses of naphthalene.

It is not my intention to develop this brief sketch any further, but I think I may say that the importance which Baeyer attached to the methods I have been describing (compare *Ber.*, 1884, **17**, 122) has been fully justified by the wide subsequent development of the Chemistry of the Closed Carbon Chains.