OBITUARY NOTICES.

WILLIAM JOSEPH ELFORD.

1900—1952.

WILLIAM JOSEPH ELFORD, who died in London on February 14th, was trained as a physical chemist and used this basic training to make a fundamental contribution to microbiology in the course of his life's work at the National Institute for Medical Research. Born at Malmesbury on January 4th, 1900, Elford early distinguished himself at the local secondary—now grammar—school and proceeded to Bristol University after a year of service with the Royal Engineers at the end of the First World War. At the University he obtained the B.Sc. degree with First Class Honours in Chemistry, and, at the same time, gained his colours at cricket, hockey, and tennis. He was elected President of the University Chemical Society and held the Colston Research Fellowship for two years. Continuing in Bristol, Elford carried out a notable piece of research for the degree of Ph.D. under the supervision of Professor J. W. McBain on equilibria underlying the soap-boiling process, and, in particular, his phase studies of the difficult binary and ternary systems potassium oleate, potassium chloride, and water have provided a model for subsequent work. Elford actually carried out many experiments on a semi-commercial scale in the soap factory, and it is a tribute to his personality that he got on extremely well both with his colleagues and with the factory people in this old and secretive industry. The antiquity of soap manufacture in Bristol is probably not well known but it may be noted that the industry there dates from the fourteenth century and the city was regarded by Fuller in his " Worthies of England " (1662), " as the staple place thereof where alone it " (*i.e.*, " gray sope ") " was anciently made." Professor McBain describes Elford's graduate work as " being distinguished by the combination of novel, elegant and optical techniques with strict physical chemical methods " and these characteristics were typical of his precise and orderly method of work throughout his life.

Elford came to the National Institute for Medical Research, then at Hampstead, in October 1925, primarily to work under the late J. E. Barnard at a time when research work on viruses was just beginning. During the next five or six years he brought to perfection his technique for ultrafiltration by demonstrating how uniform collodion membranes of accurately graded porosity could be produced and calibrated. These membranes, of an altogether different degree of accurate and uniform porosity from anything previously known in ultrafiltration, ranged in pore size from about 3 μ to 10 mμ or less, and were the first tools available for measuring the sizes of viruses. During the following decade, Elford collaborated with a number of biological colleagues in estimating the sizes of numerous viruses by graded ultrafiltration, and immeasurably accelerated progress in this difficult field by the data which these researches provided. The methods developed in the course of this work were fully summarised by Elford in an outstanding monograph which he contributed to Doerr and Hallauer's " Handbuch der Virusforschung " (1938), entitled " The sizes of viruses and bacteriophages, and methods for their determination," while a more accessible and condensed account of Elford's work in relation to ultrafiltration in general is to be found in the article by J. Douglass Ferry (*Chem. Reviews*, 1936, **18**, 373).

With the outbreak of war in 1939, Elford was drawn into researches on air-hygiene, having regard to the possible eventuality of defence against bacteriological warfare and the more directly pressing problem of the conditions obtaining in air-raid shelters. In this work his talent for careful and critical experimentation was ever obvious though it was not in keeping with his painstaking methods to come to hasty conclusions so often demanded by *ad hoc* problems. One rarely saw Elford ruffled and the nearest he ever came to showing anger was when he had convinced himself that a piece of work relating to his own fields of interest had been carried out in a slipshod manner. In 1942, he was found to be suffering from fairly severe hypertension and a poor prognosis was given. Nevertheless, having resigned himself to restriction of some of his physical activities, he was able, after a period, to resume reasonably normal work except when recurring hypertensive episodes demanded rest. In spite of uncertain health, Elford's work was not yet done and he made one further outstanding contribution to scientific knowledge, the full application of which has not yet been explored. Becoming interested in electron microscopy, he showed that the ghosts of laked fowl red cells formed suitable objects for study with this tool. Furthermore, a number of medically important viruses, including those of

influenza, were shown to be adsorbed on to these ghosts, just as they are on to the intact cells, and were then revealed by electron microscopy in some of the most beautiful and telling photographs yet obtained with this instrument.

Elford remained a bachelor and by nature he was shy and reserved. A charming manner and cheerful smile, however, made him easily approachable by all and sundry and one had no difficulty in getting to know his sterling qualities, while his assistance and advice were freely sought by many and just as freely given. He became a Fellow of this Society in 1926 and was elected a Fellow of the Royal Society in 1950.

JAMES WALKER.

GEORGE ARMAND ROBERT KON.*

1892—1951.

GEORGE KON came to British science from an unusual background. He was born in St. Petersburg on February 18th, 1892, the only child of his parents. His father was a cultured and talented member of an old Polish–Jewish family, an excellent mathematician and linguist, and the son of a portrait painter; his mother, Marie Fleuret, was French. His father was a banker in a responsible position, and the family was comfortably off. George was a delicate child and was brought up with great care and devotion by his mother and an old nurse. In the candid and penetrating autobiographical notes which he left, he remarks ruefully " It is clear that I was unnecessarily coddled and spoilt and this was to prove a handicap in later life."

He was educated privately by a succession of instructors : a French governess, two Polish tutors (one, Adolf Dygasinski, an author of some note, who gave him a love for natural history), and a German governess. When he was ten, the family moved to Tientsin in North China where his father had become manager of the Russo-Chinese Bank. He spent three happy years in China where his liking for natural history developed into a passion for butterfly collecting. He published two short notes in the *Entomologische Zeitschrift* between the ages of sixteen and seventeen.

In Tientsin he first came into contact with the people whose nationality he was to adopt and was taught English by a " worthy though hideous " lady, the daughter of a missionary. A later move was to Vladivostok, " magnificent country for shooting and ideal for butterfly collecting," and here the family made friends with Sir Robert Hodgson, then British vice-consul. The first turning point in Kon's life came when Hodgson persuaded his parents to send him to Cambridge. Accordingly, in 1909 he passed the Russian equivalent of Matriculation and, after some coaching in Greek at a rectory near Wisbech, he went up to Caius to read Medicine.

The choice of subject was his parents'; he himself wished to read Science. He " found Anatomy very dull and uphill work " but enjoyed Physiology. He failed his Second M.B. Examination but got a Second in Part I of the Natural Science Tripos in 1912. Apart from this and a rather solitary first term, Kon found life at Cambridge enjoyable. He made several good friends, played lawn-tennis and golf, and began to lose his interest in entomology and to discover one in motor-cycling. The family plans involved a business position in Russia, but on his return there he felt a stranger and decided to take up a scientific career in England. Accordingly, 1913 found him living in chambers in St. James's and attending classes in chemistry and chemical technology at the Imperial College of Science and Technology, where his fellow students included C. K. Ingold and (the late) S. Sugden.

Up to this time George Kon's career had been that of the only son of a wealthy cosmopolitan family and his scientific tastes had not crystallised. But in February a second decisive event occurred with the arrival at South Kensington of Jocelyn Thorpe, newly appointed Assistant Professor of Organic Chemistry. Kon attended his lectures " and there and then decided to become an Organic Chemist."

August 1914 found Kon in the Tyrol, but it was in a fast car and he managed to cross the Brenner before the declaration of war. He returned to England by circuitous routes and joined the team at the Imperial College engaged on the preparation of essential drugs. He worked with Miss F. M. G. Micklethwait, under whose care, he says, " I soon realised that my ideas of what work meant had to be overhauled." He was naturalised in 1916 and joined the Army as a Lieutenant in the Anti-gas Department. Among his duties were the supervision of a

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respirator factory and a liaison visit to the United States of America when they entered the war. He was mentioned in despatches in 1917, and left the army at the end of the war with the rank of Captain.

His father and mother escaped from Russia at the time of the revolution, with the loss of most of their fortune, and the reunited family set up house together in London. Later his parents moved to Paris. Kon rejoined Thorpe, worked hard with few distractions, and received his D.Sc. for a thesis, on which his examiner, W. H. Perkin junior, wrote "I approve of this publication, it is an excellent piece of work." He had now found his scientific feet and was appointed Thorpe's private research assistant in 1923 and lecturer at the Imperial College in 1925. His duties were confined to the teaching of experimental Organic Chemistry and to research supervision. The work prospered. Thorpe treated him with his habitual generosity and a long stream of important papers began to flow; these are reviewed later.

In 1926, Kon married Anne Pollock (née Watts). The marriage was dissolved in 1937. In 1930 Kon suffered financially in the Wall Street slump. These troubles were offset by his steady professional advancement and the increasing recognition of his scientific work. In 1934 he was appointed Assistant Professor at the Imperial College. He became a member of Council of the Chemical Society in 1931—32 and again in 1933—36, and served on numerous of their committees. He made admirable contributions to the *Annual Reports on the Progress of Chemistry* in 1932, 1933, and 1934. He was elected a Fellow of the Royal Society in 1943.

In 1942 he was appointed to the chair of Chemistry at the Chester Beatty Research Institute of the Royal Cancer Hospital. He had been at the Imperial College for nearly thirty years, with the break during the war. He had worked under two leading personalities of the chemical world in Thorpe and Heilbron (who succeeded Thorpe in 1938) and had kept himself largely in the background. Nevertheless his services to the College were of the greatest value in maintaining the high reputation of the Organic Chemistry school in the period between the wars. The list of his colleagues and contemporaries at South Kensington includes a formidable section of contemporary academic organic chemistry: Thorpe, Heilbron, M. A. Whiteley, Ingold, Farmer, Dickens, E. R. H. Jones, A. H. Cook, Hey, Shoppee, J. W. Baker, Rothstein, Rydon, Harper, Owen, Barton, C. E. Dent, and a large number who have made outstanding contributions in chemical industry.

He remained at the Chester Beatty Institute for the remainder of his life doing valuable work on carcinogenesis and mutagenesis. His death came very suddenly, and was a great shock to those close to him. On March 15th, 1951, an important meeting sponsored by the Chemical Society and other bodies was held in Manchester to discuss the Chemistry of Cell Division. After the introductory papers Kon opened the discussion. He referred, among other things, to the correlation between cytotoxic activity and the chemical reactivity of the nitrogen mustards. He ended on a hopeful note, saying that the structural chemical approach would certainly yield results of importance to the general problem of cancer. At the end of his speech he collapsed and died almost instantaneously from heart-failure. Few scientists can have died so immediately in action. He had had some heart trouble in the preceding months, but the suddenness of the end was sadly unexpected. He suffered from a cleft palate and public speaking placed a heavy strain on him.

George Kon was a man of remarkable gifts, and had a great range of interests outside science. An excellent linguist, he was also a connoisseur, particularly of English eighteenth century furniture and of good wine. He was wirily built and a natural athlete; a good tennis player and an enthusiastic and formidable golfer. He had a wonderful sense of rhythm which came out alike in his walk, in his games, in his chemical manipulation, and in his unusual gifts as a ballroom dancer.

With his natural elegance in manners and appearance and great personal charm, George Kon sometimes seemed to his more prosaic colleagues as a being from some other and gayer world. He became an Englishman not only by naturalisation but completely; he thought like one and joked like one. His kindliness, sincerity, and happy disposition endeared him to all those who knew him and the world indeed seems a greyer place now he is dead.

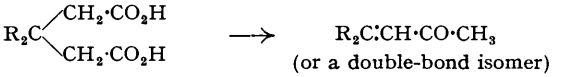
The last decade of his life was made happy by his marriage in 1938 to Mary Tress, who survives him.

Scientific work.

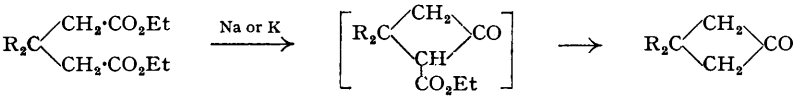
Kon's work was marked throughout by great care and quite unusual manipulative skill. He was a borne experimentalist, always happy to leave the desk for the laboratory bench. He was an expert glass-blower and a skilled analyst; almost to the end of his life he could be found

conducting his own micro-combustions. Several devices in technique and apparatus in common use today originated at his bench at the Imperial College. In interpretation and generalisation he was logical, cautious, and restrained. A good deal of his work involved repetition and re-evaluation of earlier material. The tone of his papers on controversial topics was always kindly and generous.

Kon's first research was carried out immediately after the end of the war of 1914—1919. It was a straightforward study of the neglected reaction of Guareschi, involving the condensation of cyanoacetic ester with ketones in the presence of ammonia. The results were published in a paper with Thorpe in 1919. Several important investigations followed on *spiro*-compounds. In 1921, Kon showed that the dry distillation of calcium salts of glutaric acids gave unsaturated ketones and not *cyclo*butanones :

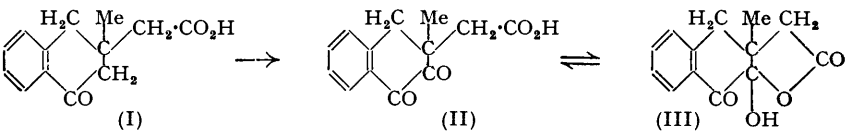


In the next year, Kon investigated the possibility of a cyclisation of the Dieckmann type on the corresponding glutaric esters. It was shown that the following reaction could occur :



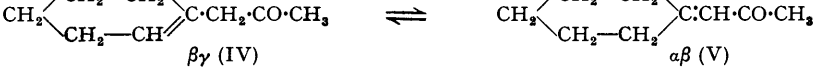
These two papers were of great value in helping to reveal the limiting structural conditions for ring formation and formed the main part of Kon's thesis for the D.Sc. of London. Other aspects of the chemistry of ring formation and of the Guareschi reaction occupied Kon during this period. With S. F. Birch and Gough the bridging of Guareschi imides was studied, and it was shown that the bridged compounds could then be degraded to *cyclo*propane compounds such as caronic acid.

Concurrent work was being carried out in collaboration with another old Cambridge man working at South Kensington, Arnold Stevenson. This led to some surprising results. It was first found that cyclisation of the Guareschi product from benzyl methyl ketone yielded the tetrahydronaphthalene derivative (I). This substance was oxidised to the diketo-acid (II) which was found to give reactions of the isomeric hydroxy-lactone (III) :



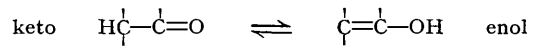
The various phenomena associated with these substances were explained on the basis of ring-chain tautomerism between (II) and (III).

The fact that the reactions of this keto-acid could not be adequately explained on the basis of a single formula put Kon on the alert for other examples of chemical ambiguity. Almost immediately one came to hand. In 1912 Otto Wallach had obtained a ketone, $C_9H_{14}O$, by condensing *cyclo*hexanone with acetone. Kon had later obtained the same substance by heating calcium *cyclo*hexane-1 : 1-diacetate. The ketone has been given the structure (IV) with the

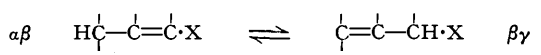


double bond $\beta\gamma$ to the functional group, mainly from the lack of exaltation in the molecular refractivity and of additive reactions with hydroxylamine and semicarbazide. On the other hand Norris and Thorpe in 1921 had found that the compound readily gave reactions characteristic of $\alpha\beta$-unsaturated ketones. Kon, Birch, and Norris accordingly re-investigated the compound. The previous ambiguous results were confirmed and amplified and it was shown that when the two distinct acid chlorides [corresponding in structure to (IV) and (V) but with Cl for CH_3] were treated with methylzinc iodide, the same ketone was obtained, which was identical with the Wallach–Kon product. The conclusion was that the two ketones were tautomeric under the conditions of formation and reaction.

These results were particularly important because they showed a practically unexplored territory and suggested the routes which exploration should take. At that time reversible isomeric changes were of course already well known, the best investigated being those of the keto-enol system :



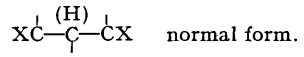
The formal tautomeric system of the Wallach–Kon ketone was of the three-carbon type :



(where X is the activating group which confers mobility).

A few other cases of reversible migration of double bonds in substituted propenes were known, notably some unsaturated αβ- and βγ-acids investigated by Fittig (X = CO_2^-) which isomerised in boiling alkali.

Wider recognition of three-carbon tautomerism had been delayed by the uncertainty over the nature of the aromatic bond. If benzene and other aromatic substances were examples of very mobile tautomeric systems which could not properly be represented by any one unsaturated structure, then it might seem reasonable to believe that among olefinic compounds some highly activated systems might be found which might have properties resembling the aromatic. There would of course be an essential difference that the aromatic systems could show no movement of an atom whereas in the propene system there would be a mobile hydrogen which would have to be accommodated somewhere in the formula. The term " semi-aromatic " had in fact been coined by Thorpe to describe the very mobile glutaconic acids, and the preferred state of the molecule was believed to be the " normal " form in which the hydrogen atom was left in an intermediate position between the α- and γ-carbons :



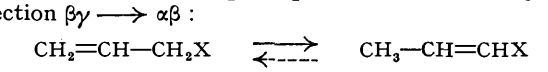
Kon might have followed this lead, particularly as the single Wallach ketone had appeared as the product of many different preparative methods. But from the first he avoided this mistake. The Wallach ketone was regarded as an ordinary equilibrium mixture of the two forms, which were too labile for isolation by the methods then available. The glutaconic acid group was put on one side for later study, and attention was immediately directed to other, less mobile, three-carbon systems. This strategy was fully vindicated. Two years later Kon and the writer discovered a pair of unsaturated ketones resembling the Wallach mixture (IV) and (V) but derived from diethyl ketone instead of *cyclo*hexanone. These two compounds could be isolated as definite individuals and their controlled inter-conversion studied. Three years after this, with Dickens and Hugh, Kon was able to isolate the two individual αβ- and βγ-forms of the Wallach ketone and to show that they readily passed into the already known equilibrium mixture. Finally, after a long study of the three-carbon system, Kon was able to turn to the glutaconic type and clarify the many puzzling features of its chemistry.

The main results of the work of Kon's school on three-carbon tautomerism are summarised below.

The movement of the double bond in an olefinic hydrocarbon usually only occurs under drastic experimental conditions. For tautomeric change to become important it is necessary for there to be present some unsaturated, electron-attracting *activating group*. The double bond can then migrate between the positions αβ and βγ to this group [as in formulæ (IV) and (V), for example]. So far as is known, double bonds in more remote positions behave like those in hydrocarbons and are comparatively non-mobile. Systems with two activating groups, αα′, αβ, or αγ are more mobile. The order of efficiency of the common activating groups is :

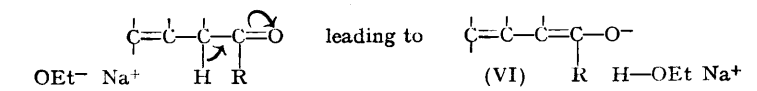
$$\left.\begin{matrix}CN\\COR\end{matrix}\right\} > CO_2R > CO^-$$

If only one such group is present in the molecule there will be a tendency for the double bond to conjugate with it, so that in the simplest possible case the migration will be virtually irreversible in the direction βγ ⟶ αβ :



For the change to become reversible, in the absence of a second unsaturated group, the βγ-form must be stabilised by alkyl substitution. This gives two products of sufficiently equal stability to undergo tautomeric change under suitable conditions.

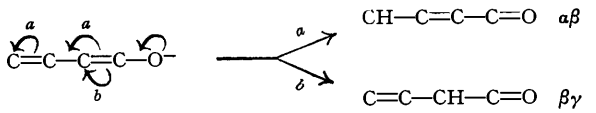
The primary process in a typical three-carbon change is the labilisation of the mobile hydrogen. This is effected by a combination of internal weakening of the carbon–hydrogen bond by an electromeric process originating with the activating group, together with the external pull of an anion or anionoid molecule. Thus for the tautomerism of a βγ-ketone catalysed by sodium ethoxide the initial stage is :



The relative efficiencies of alkoxides as catalysts depend on the acidity of the corresponding alcohols; the more acid the alcohol (that is, the more stable the alkoxide ion) the less will be its tendency to remove hydrogen in the above process. Socium *iso*propoxide is therefore a good catalyst.

The analysis of a mixture of αβ- and βγ-isomerides is generally carried out by taking advantage of the comparative inactivity of the αβ-forms towards various halogen reagents which react readily with the βγ-isomerides. The composition of a tautomeric mixture is readily found by comparison with known mixtures. In this way the *position of equilibrium* can be found. It is normally independent of the method by which it is attained although small shifts have been observed in acid-catalysed systems. The *mobilities* of three-carbon systems can be compared by a kinetic study of the velocities of change under the same standardised experimental conditions.

When the hydrogen has been removed from a tautomeric ketone (or similar substance) the residual material, as pointed out by Ingold, can be represented as the enolic ion (VI). When the hydrogen returns to this it can give rise to either the αβ- or the βγ-unsaturated keto-form. The question arises how far this recombination occurs in the alkaline medium. If the enolate were stable in the presence of the alkaline catalyst, then recombination would take place largely or wholly on the final acidification of the alkoxide solution. There is, of course, no general answer to the question. Very weak acids such as carboxylate ions or monocarboxylic esters do not enolise appreciably so that at least the bulk of recombination takes place continuously during the equilibration. On the other hand, systems with two activating groups such as α-cyano-esters are comparatively acid, and fairly stable solid sodio-compounds can be isolated. When these are acidified two possibilities arise which are represented in a simplified form below :



The question arises whether it is possible to convert sodio-compounds into the βγ-tautomerides (process *b*) without invoking the more complex process (process *a*) by which the αβ form is produced. This point was carefully studied by Kon and his co-workers and it was shown conclusively that under the right experimental conditions the enol ⟶ βγ-unsaturated ketone change could in fact be carried out with little or no formation of the αβ-unsaturated keto-form, even when the latter was the more stable isomer of the three-carbon pair. The same technique was used in Kon's first paper on glutaconic acids in 1931, and in later work in the glutaconic series Kon, particularly with E. M. Watson, was to use this method with great success.

Quantitative investigations led to the establishment of certain regularities in the effect of substitution on the speed and direction of tautomeric change. Thus in unsaturated acid systems of the type :

$$R_2C{=}CH{\cdot}CH_2{\cdot}CO_2H \rightleftharpoons R_2CH{\cdot}CH{=}CH{\cdot}CO_2H$$

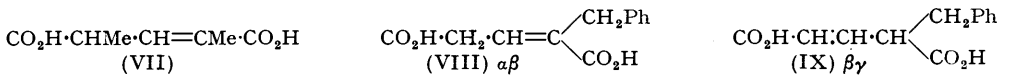
the proportion of βγ-form at equilibrium varies with R as follows :

R,R	H,H	Me,H	Et,H	Me,Me	Et,Me
Equilibrium, βγ, % ...	2	32	26	77	77

β-Alkyl groups have a similar but weaker effect, whereas an α-alkyl group stabilises the αβ-unsaturated form in acids. Unsaturated esters in general show the same results as the acids. Among unsaturated ketones β- and γ-alkyl groups give the expected stabilisation of the βγ-form but α-alkylation produces an unexpected shift in equilibrium in the same direction, that

is, it produces the opposite effect from that observed with acids and nearly all esters. There are also peculiar differences between the equilibrium data of various alicyclic systems, where the five-, six-, and seven-membered rings do not behave in a uniform manner. A considerable effort was devoted to the elucidation of the governing general rules, but the results do not lend themselves easily to summary.

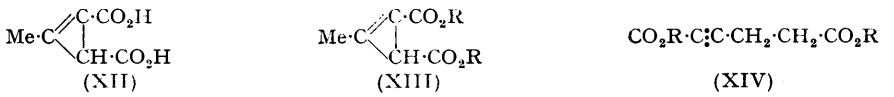
By 1931, the main factors which influence double-bond migration in carbon chains were clear. Armed with this knowledge, Kon attacked the problem of glutaconic acids. The semi-aromatic formulation for the more stable forms of these substances had just received a heavy blow in the resolution at the Imperial College of " normal " $\alpha\gamma$-dimethylglutaconic acid which accordingly had to be assigned the conventional formula (VII). Kon believed strongly that the chemistry of the glutaconic acids would have to be explicable on the basis of three-carbon tautomerism, complicated by *cis-trans*-isomerism. He used the techniques developed during the previous decade, particularly controlled regeneration from alkali derivatives and ozonolysis, coupled with careful determinations of physical constants and of halogen addition for the assessment of purity and double-bond position. The problem was rapidly solved along



these lines, although the work brought out some unexpected features. For example, α-benzylglutaconic acid can theoretically exist in two structurally isomeric forms (VIII and IX), each with two geometrical modifications. Kon found that the two acids normally encountered differed not only in configuration but also in double-bond position, being in fact the *cis*-$\alpha\beta$- and *trans*-$\beta\gamma$-forms. The stabilities of the substituted glutaconic acids vary widely with the groups present and some of the possible structures were found to be incapable of isolation. An equivalence of the α- and the γ-position in the glutaconic acid system had been postulated by Thorpe. For example, the two tricarboxylic esters (X) and (XI) had been found to yield the same γ-ethyl-α-methylglutaconic acid on hydrolysis. Kon found that this and similar phenomena were due to the high mobility of the system which led to the formation of equilibrium mixtures.

Kon's general conclusions on the structure of the isomeric acids agreed broadly with the earlier views of Feist, although the latter tended to rely on purely stereochemical explanations of isomerism and did not fully appreciate the part played by double-bond migration.

While this strong evidence was accumulating that the glutaconic acids, although complicated, were conventional three-carbon systems, a difficult problem remained to be solved. Early work on 3-methyl*cyclo*prop-2-ene-1 : 2-dicarboxylic acid (XII) had led to the proposal that the acid had the " normal " or semi-aromatic structure and that it gave rise to three series of interconvertible esters, called normal, labile, and enol. Geometrical isomerism could not be invoked to explain the existence of three esters. Kon's re-examination showed that the " normal " ester had the Δ^2-structure (XIII) and that no other ester simply derived from the acid could be isolated. The " labile " ester could indeed be formed from the " normal " ester by the action

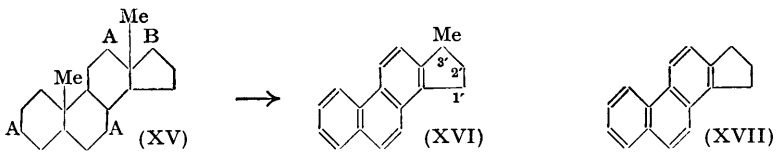


of heat but the process involved a remarkable and deep-seated change of the carbon skeleton, the product having the structure (XIV). Under the conditions believed to yield an enol ester, addition of alcohol to the double bond occurred. This careful investigation of Kon's showed that the acid and the ester (XII and XIII) did not exhibit the usual properties of three-carbon tautomers or, indeed, of glutaconic acids. The last necessity for the " normal " form thus disappeared and Kon, as he characteristically remarked, had " made honest compounds of the glutaconic acids."

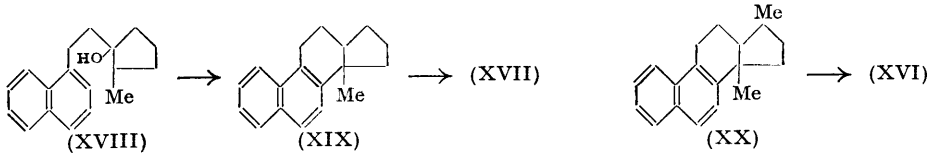
From these studies, Kon turned to a new field. The classical work of Wieland, and of Windaus, had begun to bring out of the mists the chemical nature of the steroids and bile acids. Structural formulæ for cholesterol and other key compounds were advanced. After some uncertainty the belief grew that the steroids were based on the tetracyclic structure (XV)

where A may be hydroxyl groups and B is a variable side chain. We may note that this structure has very recently been confirmed by several total syntheses.

In 1933 a key compound in the structural analysis was the " Diels hydrocarbon," $C_{18}H_{16}$. Diels had prepared this by the dehydrogenation of cholesterol and ergosterol. At first it was thought to be a hydrochrysene. Subsequently a structure based on *cyclo*pentenophenanthrene (XVII) was favoured. Elementary analysis did not permit a clear distinction between *cyclo*pentenophenanthrene itself (XVII), $C_{17}H_{14}$, and a monomethyl derivative, $C_{18}H_{16}$, such as (XVI). *cyclo*Pentenophenanthrene (XVII) was accordingly synthesised by Kon, and simultaneously and independently by L. Ruzicka and by J. W. Cook and their co-workers. The synthetic material was very similar to the Diels hydrocarbon but there were differences between the derivatives, and the crystallographic evidence of Bernal and Crowfoot finally showed that they were not the same. On the other hand the resemblances, particularly in absorption spectra, were so close as to encourage belief that they were nearly identical in structure. Kon accordingly, with S. H. Harper and F. C. J. Ruzicka, undertook the synthesis of the 3′-methyl compound (XVI). For this Kon used the following approach, typical of his care and good sense. 2-Methyl*cyclo*pentanone was found to react with the Grignard compound from 2-α-naphthylethyl bromide to yield the alcohol (XVIII). Cyclisation of this with phosphoric oxide gave a tetracyclic hydrocarbon which yielded *cyclo*pentenophenanthrene (XVII) on dehydrogenation, with elimination of the methyl group. Hence its structure must have been (XIX). The sequence of reactions was then repeated, 2 : 5-dimethyl*cyclo*pentanone being used



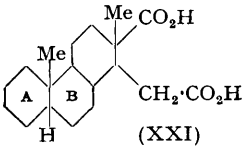
as starting material. The penultimate hydrocarbon was (XX) and its dehydrogenation gave 3′-methyl*cyclo*pentenophenanthrene (XVI). The synthetic compound was found to be identical in physical and chemical properties with the Diels hydrocarbon. Simultaneously and independently Bergmann and Hillemann prepared the 3′-methyl compound by a different process but did not establish its identity with the Diels compound. Rigorous further examination by Kon, and in the other laboratories concerned, showed that all three substances were the same. 3′-Methyl*cyclo*pentenophenanthrene was thus proved to be an important product of the dehydrogenation of cholesterol. This was a major piece of evidence in establishing the structure of the steroids on their present firm basis.



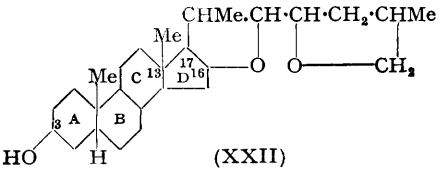
Although Kon was to publish several other papers on synthetic topics related to steroids they were of less importance than the successful coup which had just been described. In 1935—36 his interest turned to a group of the natural steroids themselves—the steroid sapogenins. From them he was led into the related sapogenins of the triterpene group. He worked on these two classes of sapogenins for 6—7 years.

Steroid sapogenins have recently been the subject of considerable study, partly because of the possibility of their conversion into the sex hormone, progesterone. At the time Kon began to work in the field there were several pieces of evidence connecting them in structure with the steroids. In particular, Tschesche had degraded tigogenin (from *Digitalis*) to *ætio*-5-*allo*-bilianic acid and thus connected it securely with the normal sterols of the cholestane series, in which rings A and B are fused in the *trans*-configuration. Kon carried out a similar degradation on sarsasapogenin acetate. The end-product was *ætio*bilianic acid (XXI) identical with a well-known breakdown product of the bile-acid group. From this result and from an earlier comparison of the behaviour of *Digitalis* and sarsaparilla sapogenins as surface films (with Askew and Farmer), Kon proposed the formula (XXII) for sarsasapogenin, making it into a geometrical isomeride of Tschesche's tigogenin.

During this work Kon isolated from Jamaica sarsaparilla root an isomeric genin which he called smilagenin. He subsequently connected this with sarsasapogenin in a manner which established that the difference between them lay in the configuration of the side-chain attached to $C_{(16)}$ and $C_{(17)}$. Recent work by Marker has led to a modification of the Tschesche formulation of the side-chain and the accepted partial formulæ for sarsasapogenin and smilagenin today are (XXII*a*) and (XXII*b*) respectively, the remainder of the molecule being as in (XXII). Kon's work established for the first time the existence of two typical kinds of isomerism of the



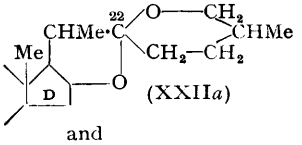
(XXI)



(XXII)

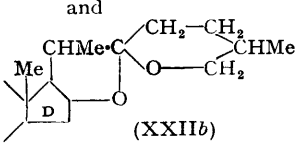
steroid sapogenins; namely that of the A/B ring fusion, and that in the side-chain at $C_{(22)}$. In later work, Kon with Woolman fixed the $C_{(3)}$ position of the hydroxyl group in sarsasapogenin. He also isolated a new sapogenin from the seed kernels of *Bulanites aegyptica*.

The more complex triterpene sapogenins next claimed his attention. These substances occur in various plant materials in the form of their glycosides, the saponins. They contain thirty carbon atoms and those of known structure have five alicyclic rings. They are closely related in structure to a number of other triterpenes which occur free in various plant resins, saps, and barks. With one or two exceptions the triterpene sapogenins of known structure are related to one triterpene, β-amyrin, the accepted formula for which, due to R. D. Haworth, is (XXIII). A distinguishing characteristic of these triterpenes is that on dehydrogenation they yield a mixture of aromatic compounds made up of sapotalene (1 : 2 : 7-trimethylnaphthalene), 1 : 8-dimethylpicene, and other materials.

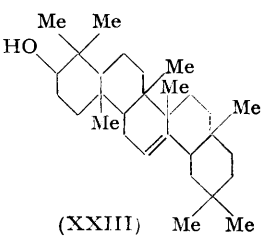


(XXII*a*)

and

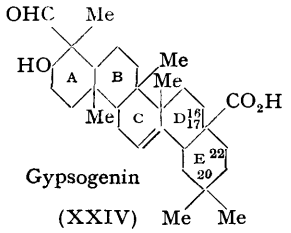


(XXII*b*)

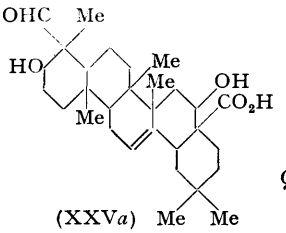


(XXIII)

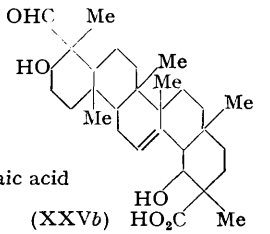
Many plants belonging to the *Caryophyllaceae* contain rather large amounts of saponins. That from *Gypsophila* (soapwort) had been hydrolysed to the sapogenin, gypsogenin, and the structure of this had been shown by L. Ruzicka to be (XXIV). Its connection with two other sapogenins hederagenin and oleanolic acid had been established. Kon selected a second member of the order in fuller's herb (*Saponaria officinalis*). From the root of this a saponin was obtained which on hydrolysis yielded gypsogenin identical with that made by Ruzicka. Kon also reviewed Wedekind's examination of the sapogenin (" githagenin ") from corncockle and came to the conclusion that it also was identical with gypsogenin. He suggested that this genin may be characteristic of the *Caryophyllaceae*.



(XXIV)



(XXV*a*) Me Me

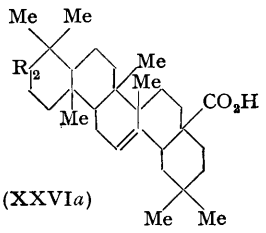


(XXV*b*)

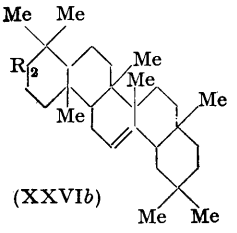
A compound of related structure is quillaic acid, on which Kon published several valuable papers. This is a fairly accessible triterpene as quillaia saponin (from soapbark) is used in commerce. A possible structure was shown to be that of a hydroxygypsogenin. Kon's

experimental results, which included measurements of the areas of unimolecular surface films, were first interpreted on the basis of a $C_{(16)}$-hydroxyl group, a *trans*-locking of rings D and E, and a $C_{(17)}$-carboxyl group (XXV*a*).

In later experiments the unimolecular film technique was applied to a number of other triterpene sapogenins containing acidic or ester functions. This involved studies of the conversion of oleanolic acid (XXVI*a* or *b*; R = OH) successively into the 2-keto-acid (oleanonic) and the deoxy-acid (γ-oleananic acid). The measured unimolecular film areas of these molecules differed from those expected on the basis of the Haworth formula. Kon was therefore led to propose that the carboxyl group in these triterpene acids was in a terminal ring. The $C_{(20)}$-position was selected as the most probable, which would lead to structure (XXVI*b*; R = OH) for oleanolic acid, and (XXV*b*) for quillaic acid. Later papers by Kon with Bilham and W. C. J. Ross produced further physical evidence in support of the $C_{(20)}$-position of the carboxyl group. For example, film measurements on derivatives of β-boswellic, ursolic, and betulic acids agreed with the view that the carboxyl, the only polar group, was at the end of the molecule. An examination of glycyrrhetic acid, the sapogenin of liquorice root, also led to results consistent with the new position for the carboxyl group. On the other hand the ready lactonisation of oleanolic acid observed by Ruzicka's school agreed better with the Haworth formula (XXVI*a*; R = H), and necessitated a modification of the formula proposed by Kon.



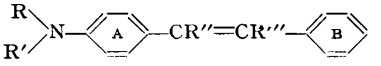
(XXVI*a*)



(XXVI*b*)

Although Kon's proposals were consistent and well argued it now appears that the surface film measurements do not provide a safe diagnostic method in this series. Recent work, particularly by Barton and E. R. H. Jones, provides strong support for the original Ruzicka–Haworth structures, of the type (XXVI*a*) and (XXV*b*), and the $C_{(17)}$-position of the carboxyl group is generally accepted today.

Kon's work in the sapogenin field ended in 1942, on his appointment to the Chair at the Chester Beatty Research Institute of the Royal Cancer Hospital. His introduction to chemical carcinogenesis came towards the close of a phase in that subject which had lasted for some fifteen years, and during which Kennaway, Cook, Hieger, Hewett, and others had established the importance of the polycyclic aromatic hydrocarbons. Although Kon had earlier been indirectly associated with these researches through his syntheses of *cyclo*pentenophenanthrene and Diels' hydrocarbon, his immediate contributions were at first limited to studies of various hydrocarbons and hydroxylated derivatives—*e.g.*, the isomeric propenylnaphthalenes, and the important metabolite 8-hydroxy-3 : 4-benzopyrene—in relation to the mechanism by which carcinogenic compounds are detoxified in the animal body. Soon, however, there arose a fresh and major development through the discovery of carcinogenic activity in 4-aminostilbene. Thereafter Kon played a leading part in an extended and fruitful investigation (with A. Haddow, R. J. C. Harris, and Edna M. F. Roe) whereby the main features of this structure (XXVII), *viz.*, the polar group, the ethylene bridge, and the nuclei A and B, were modified in such a way



(XXVII)

as to shed much light on the relations within this series of chemical constitution and biological action. The great majority of the biologically active compounds proved to be stilbenes with a basic substituent, the position of which was of paramount importance, *o*-dimethylamino-stilbene, for example, being very much less active than the *p*-isomeride, and the *m*-compound completely inactive. Activity was further shown to depend on the integrity of the ethylene bridge, since it disappeared when either of the hydrogen atoms was substituted, when the bridge was reduced, when it was extended to contain three or more carbon atoms, when either methine group was replaced by a nitrogen atom, or when the bridge itself was absent or was replaced by oxygen or sulphur. Activity was also dependent on the *trans*-configuration of the molecule

about the ethylenic bond, and to a large extent on a free *p'*-position. These and other facts suggested the working hypothesis that one of the features required for activity was an unbroken conjugation of the amino-group with both nuclei, enabling the compound to assume some dipolar quinonoid character depending, among other things, on the co-planar arrangement of the two benzene nuclei which characterises the *trans*-form of the stilbenes. When evidence concerning steric conditions was compared with the biological activities of these compounds, a close parallel was suggested between lack of activity and buckling of the molecule. Thus in the inactive 4-dimethylaminostilbene derivatives with substituents on the α- and β-carbon atoms of the ethylenic double bond, or with methyl groups at two *ortho*-positions in a phenyl group, steric factors reduce the planarity of the molecule, so affecting the conjugation resonance characteristic of the molecule as a whole. All the evidence from diagrams, models, and spectra suggested that steric interference with the planar configuration in this series varies continuously from the planar 4-dimethylaminostilbene to the highly buckled αβ-diethyl derivative. Hence it appeared, in short, that biological activity within this series depends on a conjunction of such factors as molecular size and shape, and the apposition of a planar molecule to a hypothetical receptor surface. Kon obtained a great deal of satisfaction from this relatively complete study, and it is of interest that the foregoing conclusions have in general been supported by a more recent investigation by L. E. Sutton and others involving measurement of the electric dipole moments.

Kon next made an outstanding contribution to yet another development, with which he was still very actively concerned at the time of his death, namely, a study of the cytotoxic action of various new series of halogenoalkylarylamines (" aromatic nitrogen mustards ") and the discovery of their carcinogenic action. Although this investigation originated in an attempt to augment the cytotoxic and therapeutic action of the chloroethylamines, and especially to determine in what types of aromatic amine the *NN*-di-2-chloroethyl side-chain could still contribute its specific cytotoxic properties, it rapidly developed along unexpected lines to yield much fundamental information. It soon became obvious, as had been suspected by others for the aliphatic series, that cytotoxic activity depended on the presence in the molecule of two halogenoalkyl groups. It was this feature which led three of Kon's junior colleagues—namely, R. J. Goldacre from the general aspect of adsorption of drugs to protein, A. Loveless from the standpoint of chemical cytology, and W. C. J. Ross from a consideration of the kinetics of reaction of such two-armed compounds—to formulate what could be regarded as among the simpler possible explanations, that such substances might produce their cytotoxic effects in general, and various characteristic chromosomal and mitotic abnormalities in particular, through a process of cross-linkage between the constituent linear macromolecules of the chromosomes themselves. The new hypothesis soon led (partly owing to a suggestion from J. B. Speakman) to the synthesis by Kon and his colleagues of a series of diepoxides related to those previously employed as cross-linking agents in various textile applications, and to their subsequent biological test. These were the first of a number of chemical types all yielding the same carbonium ion, and at once it became evident that they were able to produce cytotoxic effects largely indistinguishable from those due to the di(halogenoalkyl)amines themselves; several, including the simplest of the series, namely 1 : 2-3 : 4-diepoxybutane, later proved to be carcinogenic as well. Although the cross-linking hypothesis is now known to represent an unduly simplified interpretation, and other possibilities are equally likely, it has in fact proved immensely fertile in development, and there can be no doubt of the significance for chemical carcinogenesis that these agents, and others discovered later, may operate by the biological alkylation of genetic protein. As can well be imagined, Kon took the greatest interest in these and related developments, and was ever ready to assist, whether by generous encouragement or a wise and kindly criticism. As has already been indicated, his death occurred immediately after he had opened the discussion at a meeting on " The Chemistry of Cell Division " held on March 15th, 1951, in Manchester. In his introduction Kon had stressed the satisfactory correlation between cytotoxic activity and the degree of purely chemical reactivity of the " nitrogen mustards " as measured by hydrolysis rates. On the question whether the effect of chain length could be attributed to steric or to polar factors, the answer seemed to him to be fairly clear, namely, that the two ends of the chain could be separated within limits, but that if the distance of the terminal carbon atom from the nitrogen atom was much increased beyond two carbon atoms, the activity fell off sharply, as did the rate of hydrolysis. If, however, this separation was achieved by inserting CH_2 groups between two nitrogen atoms so placed as to exert their polar effect and favour the production of a carbonium ion, the lengthening of the chain effected but little decrease in biological activity. Kon concluded that he had

every hope from all this work of eventual results with a very positive bearing on the cancer problem as a whole. Whether or not such will prove to be the case—and it is probable—his own contributions, together with those of his earlier career, ensure him a lasting and an honoured place not only in pure chemistry and the chemistry of natural products, but also in chemistry in its modern relation to biology and medicine.

In the preparation of this notice I have been greatly helped by Mrs. Mary Kon and by Professor A. Haddow. Professor Haddow very kindly reviewed the work done at the Chester Beatty Institute.

R. P. LINSTEAD.

J. R. PARK.

1902—1952.*

BRITISH applied science has suffered a severe loss in the untimely death, on July 30th, 1952, of Mr. J. R. Park, a Managing Director of the British Oxygen Company. Mr. Park was born in London in 1902 and was educated first at Battersea Grammar School and then at Queen Mary College where he graduated in chemistry. After a short period on the staff of Westminster Technical College he worked as an analytical chemist in industry for a number of years in Britain, and then for a year in a French firm.

In 1929 he joined Imperial Chemical Industries Limited, Billingham Division, where he remained until 1945. For a time he worked there as a plant manager, but soon he moved to the research side. The production of hydrogen, hydrogenation of coal, synthesis of ammonia, and synthesis of methanol were some of the fields which occupied him in the years up to the war; he had by then advanced to the position of Ammonia Research Manager. He was also connected with the design of oil hydrogenation plant and in the first year of the war was responsible for the design of various other plants. The writer made his acquaintance in 1941, when Park was put in charge of the Billingham research team working on the British Atomic Energy Project. His quick grasp of problems, his strong scientific background, and his understanding of large-scale industrial processes formed a combination that contributed greatly to the success of the enterprise.

In 1945 Park was asked to organise a research department in the British Oxygen Company. He did this with outstanding success, creating within a few years a large and flourishing research organisation practically from scratch. His worth was quickly appreciated; in 1948 he became Assistant Managing Director, and soon was promoted to the post of Managing Director. It is largely due to Park that the British Oxygen Company has been transformed from an undertaking relying mainly on foreign patents into a modern enterprise standing on its own feet in the field of research and development. Park was one of the all too small group of first-class British chemical technologists who are essential for the economic future of this country; his death leaves a gap which will be felt for a long time. His friends mourn the passing of a personality of wide interests and great charm, and of a warm-hearted and loyal companion.

Park became a Fellow of the Society in 1945 and was a member of the Finance and General Purposes Committee from 1948 to 1952.

F. E. SIMON.

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