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Leningrad Institute of Technology

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THE WOLFF REARRANGEMENT

L. L. Rodina and I. K. Korobitsyna

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I. INTRODUCTION

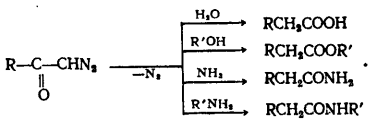
The great reactivity and comparatively ready accessibility of α-diazo-ketones have contributed to the rapid development of the chemistry of this peculiar class of organic compounds — see the most important reviews[1-11].

Many methods are now available for the preparation of α-diazo-ketones, the most important of these being the Arndt–Eistert method[12-38], consisting in the interaction of acid chlorides or anhydrides with excess of diazomethane, and the Curtius method, which is in effect the oxidation of monohydrazones of α-diketones with yellow mercury(II) oxide[39-47] or with some other oxidant[48-51]. Other derivatives of α-diketones — e.g. the toluene-*p*-sulphonylhydrazones[52-60] and the mono-oximes[61-63] — can also be used to obtain α-diazo-ketones. A new method had recently been worked out for the synthesis of α-diazocarbonyl compounds from alkane- or arene-sulphonylazides and carbonyl compounds[64-70].

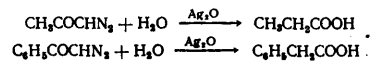
Among the various transformations undergone by α-diazo-ketones, the Wolff rearrangement is of most interest. The great amount of information which has accumulated in the more than 50 years since its discovery, the large quantity of experimental results obtained during recent years, and also the absence of reviews dealing specially with this question have led us to write the present paper. The literature is surveyed up to 1964 inclusive, and partly for 1965.

II. DEFINITION AND MECHANISM OF THE WOLFF REARRANGEMENT

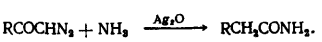
The Wolff rearrangement — the conversion of α-diazo-ketones into acids and their derivatives — takes place on heating, in the presence of catalysts, or on ultraviolet irradiation in the presence of water, alcohols, ammonia, amines, etc:



In 1902 Wolff, while studying the properties of diazo-ketones[71,72], found that diazoacetone and diazoacetophenone, on interaction with water in the presence of silver oxide, did not undergo the usual replacement of the diazo-group by hydroxyl with formation of a hydroxy-ketone, but instead suffered rearrangement, with formation of propionic and phenylacetic acids respectively.



He showed in the same paper that, with aqueous ammonia to which a small quantity of silver oxide or silver nitrate had been added, diazo-ketones yielded amides even in the cold:



Independently of Wolff, in 1909 Schroeter.[73,74] observed an analogous rearrangement with "azibenzil" (benzoylphenyldiazomethane), and some authors therefore employ the term "the Wolff–Schroeter rearrangement".

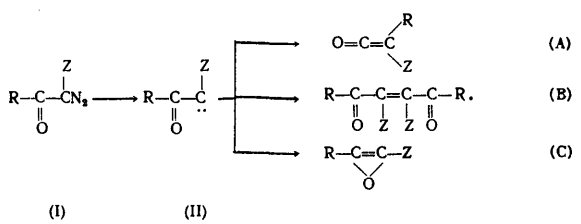
Catalytic rearrangement was employed mainly in the early work, the catalyst being most often silver oxide or a silver salt[72,75]. Finely divided platinum[72] and copper[76] are used considerably less frequently. With copper, however, the Wolff rearrangement takes place under severe conditions, the yield of acid being sharply diminished owing to the formation of other reaction products, mainly diacylethylenes[77-86]. An exception is provided by copper(I) iodide, with which rearrangement can occur under milder conditions[87].

The thermal rearrangement of α-diazo-ketones is employed less often than the catalytic method, for with the more severe conditions there is risk of decomposition of the starting materials. Nevertheless, this method of rearrangement gives very good results in the preparation of acid derivatives — anilides and certain esters[75,88,89].

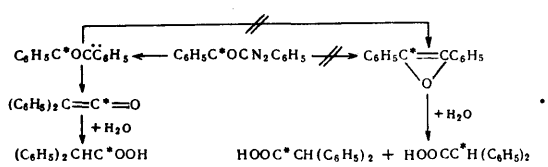
The considerable advantages of photolysis[90] as a method of effecting the Wolff rearrangement — the mild conditions for the reaction, the practical simplicity, and the possibility of considerably shortening the subsequent operations of separation and purification of the products — have rapidly brought it to the fore during recent years.

The mechanism of the Wolff rearrangement has now been studied quite fully. Wolff himself regarded the detachment of nitrogen as the cause of the reaction which he had discovered[71,72]: the residue remaining after detachment of nitrogen from the diazo-ketone molecule contains free valencies on the carbon atom, and undergoes rearrangement into a keten, which interacts with a hydroxy- or an amino-compound present in the reaction mixture to given an aicd or a derivative thereof.

The many subsequent investigations have convincingly shown that the first stage in the Wolff rearrangement is detachment of nitrogen from the diazo-ketone (I), accompanied by intermediate formation of a carbenone (II):

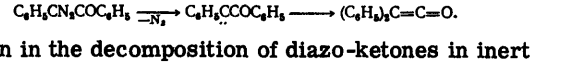


The defective octet in the intermediate compound (II) can be completed in three different ways — (A), (B), and (C) — the transition (II) → (A) resulting in formation of a keten, and from the latter the acid or its derivative, so that it represents the normal Wolff rearrangement. The bimolecular reaction (II) → (B) occurs comparatively rarely with diazo-ketones (for furthere details see Section V, 2). It usually takes place when R is a donor group, e.g. ethoxyl: thus, under the conditions of the Wolff rearrangement, diazoacetic ester is readily converted into diethyl fumarate[91]. Franzen has proved that formation of an oxiren (II) → (C) is not an intermediate stage in the Wolff rearrangement[92]. He effected the photochemical and thermal decomposition of azibenzil containing a labelled carbon atom in the carbonyl group, and showed that stabilisation of the carbenone occurs by migration of a phenyl group with formation of diphenylketen; the latter interacts with water to form diphenylacetic acid in which the whole of the activity is concentrated in the carboxy-group:

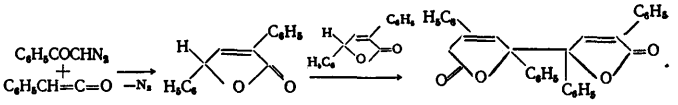


Thus the transformation (II) → (A), i.e. the Wolff rearrangement, is to be expected when R represents a hydrocarbon radical.

The intermediate formation of ketens in the rearrangement of diazo-ketones has in several cases been demonstrated experimentally [73,93-95]. Thus Schroeter isolated diphenylketen in the thermolysis of azibenzil in an aprotic solvent [73]:

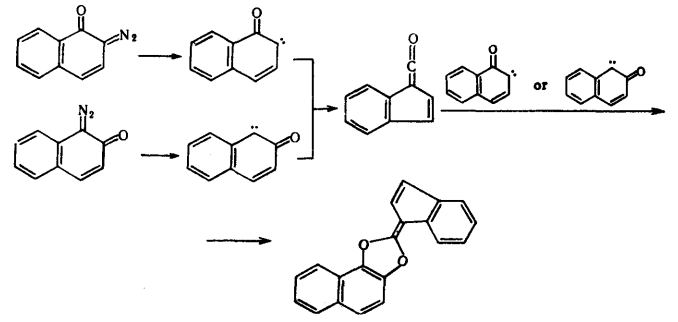


More often in the decomposition of diazo-ketones in inert solvents, however, ketens themselves are not obtained, but products of their further transformation, which is explained by the tendency to polymerise [96], and also to interact with the initial diazo-ketones or with the carbenones resulting from detachment of nitrogen from them. Thus the thermolysis of α-diazoacetophenone in dodecane led to the formation of a dilactone, to which has now been assigned the following structure [97]:



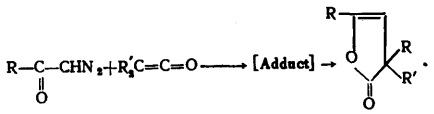
The formation of this compound is explained by interaction between the keten resulting from the rearrangement and the intermediate carbenone [98-100].

An analogous process obviously takes place in the thermal decomposition of diazonaphthaquinones [101]:

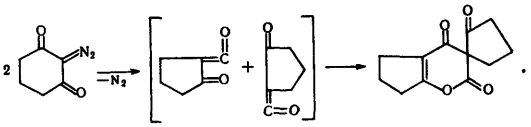


and in several other cases [102-105].

The interaction of ketens with diazo-ketones leading to the formation of βγ-unsaturated lactones is reported by Ried and Mengler [106-108], who assume that a short-lived addition product is produced, and stabilises itself by splitting off a molecule of nitrogen to give the unsaturated lactone:

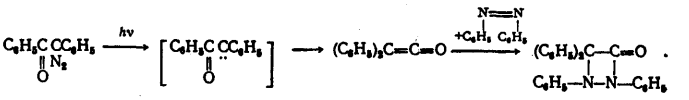


An interesting result has recently been obtained by Stetter and his coworkers [109] in the thermolysis of 2-diazocyclohexane-1,3-dione in xylene:

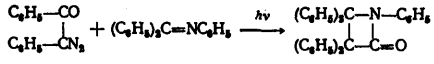


Formation of the final reaction product can be explained only by Wolff rearrangement of the initial diazo-ketone followed by dimerisation of the resulting keten.

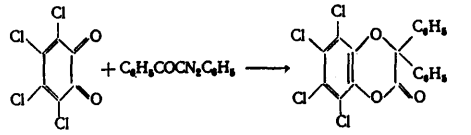
The formation of ketens during the Wolff rearrangement has been demonstrated in many cases by their reactions with specially added reagents. When azibenzil is illuminated in the presence of azobenzene, for example, a crystalline adduct is obtained which is a derivative of 3-oxodiazetidine [93]:



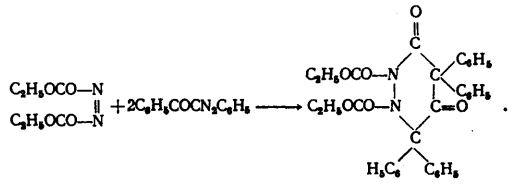
Cook and Jones [110] obtained the same compound from diphenylketen and *cis*-azobenzene. Ketens can add on also to azomethines (Schiff bases) to give β-lactams [111]:



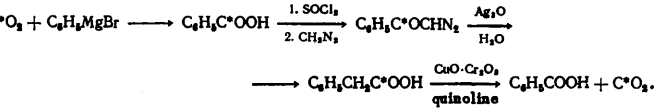
The keten arising in the photolysis of azibenzil could be recovered also by reaction with tetrachlorobenzo-*o*-quinone [93]:



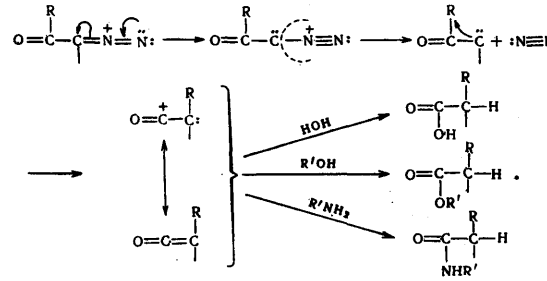
and by illuminating azibenzil together with azoformic ester [112]:



Conversion of the carbonyl group in a diazo-ketone into a carboxyl is established beyond doubt by the following cycle of reactions, in which radioactive carbon has been used [113]:

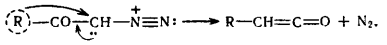


Thus the mechanism of the Wolff rearrangement can be represented by the scheme



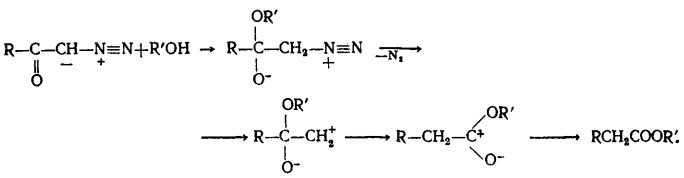
In the first stage, decomposition of the diazo-ketone with elimination of nitrogen results in the appearance of a carbenone characterised by an electron deficit. The carbenone is stabilised by the attack on a pair of electrons forming the β-bond. Depending on the reaction conditions, the resulting keten is converted into an acid, an ester, or an amide. Consequently the Wolff rearrangement represents a particular case of a large number of nucleophilic rearrangements occurring in saturated systems.

In the opinion of some authors[1], however, the carbenone structure is incompletely realised in the Wolff rearrangement, since transfer of the carbanion is assumed in several cases to occur synchronously with elimination of the nitrogen molecule:



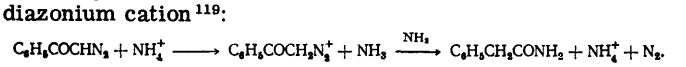
During the rearrangement of benzoylphenyldiazomethane in the presence of alcohol, an ether of benzoin is formed as a side-product[114] (i.e. the nitrogen molecule is eliminated before the rearrangement occurs). In some cases formation of oxidation products of the intermediate carbene is observed[115-117]. Both facts contradict the synchronous mechanism.

Müller formulated the following mechanisms for the rearrangement of diazo-ketones in the presence of an alcohol or water[118]:



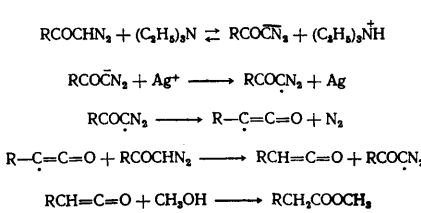
However, evidence is lacking for the intermediate formation of a betaine.

Other mechanisms have been suggested for the Wolff rearrangement. Thus Baddeley et al. consider that the rearrangement involves the intermediate formation of a diazonium cation[119]:



Such a mechanism is open to question, since the rearrangement of diazo-ketones is usually accomplished in neutral or even in weakly alkaline medium, where the appearance of a diazonium cation is improbable. Nevertheless, in isolated cases, when rearrangement occurs in acid medium[120,121], the possibility that a diazonium cation may be formed cannot be completely denied.

Newman and Beal[122], who were successful in effecting the Wolff rearrangement in homogeneous medium (in methanol in the presence of silver benzoate and triethylamine)[123-125], consider that under these conditions the rearrangement has a chain mechanism:

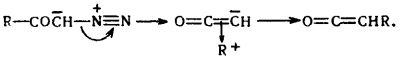


In their opinion this is supported by the following results: (1) reaction does not occur with diazo-ketones of the type $RCOCN_2CH_3$, which indicates that hydrogen must be present on the α-carbon atom; (2) reaction ceases on the addition of quinol, this obviously being due to reduction of the silver ion or of one of the intermediate products (reaction starts afresh on addition of excess of a silver salt); and (3) the reaction does not go in the absence of triethylamine, which confirms the first stage in the above mechanism.

The possibility of a radical mechanism for the rearrangement of diazo-ketones is consistent with the fact that other examples of homolytic,1,2-rearrangements have recently been discovered[126-131]. It must be stressed, however, that this mechanism is possible only under the above conditions and only with diazo-ketones in which hydrogen is attached to the carbon atom adjacent to the diazo-group.

The generally accepted mechanism for the Wolff rearrangement, implying intermediate formation of a carbenone which rearranges into a keten, is evidently the most probable.

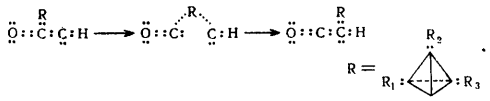
It is interesting that Dewar[132] suggested that the intermediate compound has the classical form of a π-complex:



This is consistent, in his view, with the fact that the Wolff rearrangement is an intramolecular rearrangement.

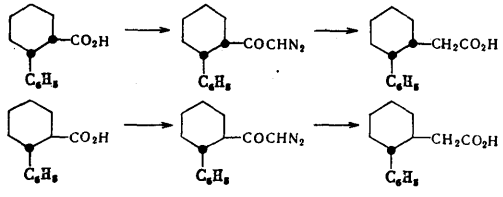
III. STEREOCHEMISTRY OF THE WOLFF REARRANGEMENT

A fundamental part of the mechanism of the rearrangement is the migration of the group R to an adjacent carbon atom. It might be supposed that during this process the group R would exist for a very short time as a kinetically independent particle. In order to assess the hypothesis critically, certain optically active compounds, in which R contained an asymmetric carbon atom, were subjected to the rearrangement. There could be three possibilities in such reactions: (1) racemisation might occur during the rearrangement, so that an optically inactive product would be obtained: (2) the compound might maintain its activity and configuration; or (3) while optical activity was preserved, there might be a change in configuration: i.e. Walden inversion might occur. Numerous investigations have established that, when optically active compounds undergo the Wolff rearrangement, the products are also optically active[133-139]. The retention of optical activity most probably means that the migrating group cannot exist in a free state even for a short period, but always remains within the force field of the molecule; while its bond with the adjacent carbon atom is still not completely ruptured, the group comes under the influence of another carbon atom, which prevents a change in configuration. This effect can be represented by the scheme[140]

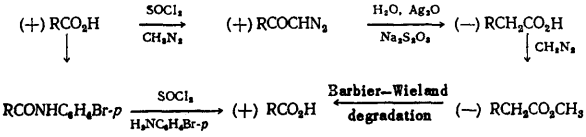


The above scheme gives a real idea of the migration of a pair of electrons from one carbon atom to another

(internal redox process). Such formulation of the process assumes the displacement to be strictly intramolecular (at no time does the system dissociate into either neutral or charged fragments). Under these conditions an optically active group should not be racemised in the course of the rearrangement. Moreover, inversion of configuration cannot occur with this formulation[141,142]. Thus Gutsche showed that configuration is maintained in the rearrangement of diazo-ketones obtained from *cis*- and *trans*-2-phenylcyclohexanecarboxylic acids[143]:

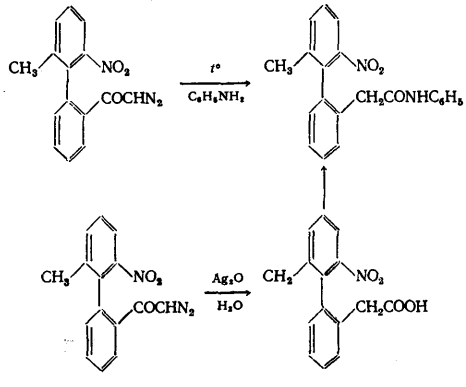


Lane[140] demonstrated the retention of configuration in the rearrangement of the diazo-ketone from (+)-2-methyl--2-phenylhexanoic acid, which was converted by the Arndt–Eistert method into optically active 3-methyl-3-phenylheptanoic acid. This was converted back, by Barbier–Wieland degradation, into the original acid. In this cyclic process initial and final products had the same optical rotation:



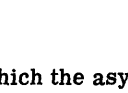
where R = n-$C_4H_9C(CH_3)(C_6H_5)$–.

The same worker showed[144] that, on thermolysis in boiling aniline, optically active diazomethyl 2′-methyl--6′-nitrobiphenyl-2-yl ketone gives without racemisation optically active 2′-methyl-6′-nitrobiphenyl-2-ylacetanilide. Rearrangement of the same diazo-ketone in aqueous–alkaline solution in the presence of silver oxide gave the optically active acid, which was then converted into the corresponding optically active anilide, found to be identical with the first anilide:



If the migrating group were able to detach itself even for an instant during the rearrangement, the blocking effect would have been removed, so that free rotation would have become possible, and racemisation would have occurred. Thus the possibility is eliminated of explaining the retention of optical activity by the presence of a free pair of electrons, which could act as a fourth substituent and prevent racemisation.

It is true that Bell[145] put forward the hypothesis that the radical may exist for a relatively short period in comparison with the time required for rotation of the two aromatic rings. It must be remarked that, if dextrorotatory 1-diazo-3-methyl-4-phenylbutan-2-one is subjected to the Wolff rearrangement, partial or complete racemisation (depending on the experimental conditions) takes place[146]. This phenomenon can be explained by the peculiar properties of the diazo-ketones



in which the asymmetric centre contains a mobile enolising hydrogen, since study of the behaviour of optically active diazo-ketones of the type

(where R_1, R_2, and R_3 are alkyl or aryl groups) under conditions of the Wolff rearrangement showed no trace of racemisation.

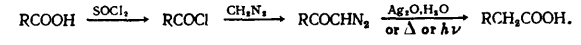
It must be emphasised that, when a secondary asymmetric atom is present, racemisation is observed usually in cases in which the Wolff rearrangement is conducted at temperatures exceeding 180° or in the presence of a catalyst, this obviously being due to tautomerisation of the diazo-ketone before rearrangement. The photolysis of diazo-ketones enables the Wolff rearrangement to be accomplished in the absence of a metal catalyst, and thus racemisation to be avoided during the reaction. Thus Wiberg and Hutton[147] established that, on ultraviolet irradiation, 1-diazo-3-methyl-4-phenylbutan-2-one gives mainly a rearrangement product in which the configuration is maintained.

IV. CHIEF SYNTHETIC APPLICATIONS OF THE WOLFF REARRANGEMENT

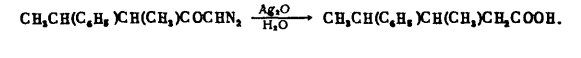
The Wolff rearrangement is of quite general synthetic value, being widely applicable for the preparation of acids and their derivatives in the aliphatic, aliphatic–aromatic, aromatic, alicyclic, and heterocyclic fields. It is successfully employed also for ring contraction.

1. Wolff Rearrangement as a Method of Synthesising Homologous Acids

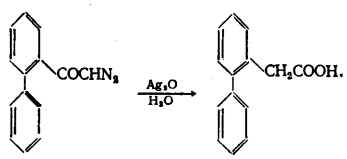
The Wolff rearrangement constitutes one stage in the Arndt–Eistert synthesis of homologous acids[19,75,148–152]:



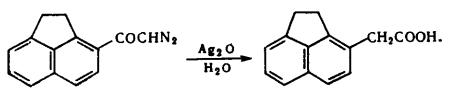
Thus, for example, an 81% yield of β-methyl-γ-phenylvaleric acid has been obtained by decomposing the corresponding diazo-ketone in the presence of silver oxide[153]:



Biphenyl-2-ylacetic acid has been obtained in 68% yield under the same conditions from biphenyl-2-yl diazomethyl ketone[154]:



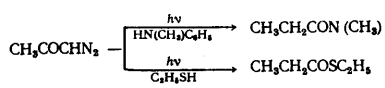
Acenaphthen-3-ylacetic acid is formed in approximately the same yield[155]:



The decomposition of diazo-ketones need not be conducted in aqueous medium: it is possible, and often even advisable, to effect the reaction in alcohol or aniline, since the rearrangement of diazo-ketones into acid derivatives usually occurs with rather better yields[65,156-161]. Ammonia and amines, especially aniline, add most smoothly, while the reaction goes less well with water and alcohols. Thus a 7% yield of *o*-nitrophenylacetanilide is obtained from diazomethyl *o*-nitrophenyl ketone, whereas ethyl *o*-nitrophenylacetate is obtained in 60% yield[162]. 1-Naphthylacetamide had been isolated in 84% yield from the corresponding diazo-ketone, whereas the yield of 1-naphthylacetic acid varies from 50% [162] to 70%.[27]

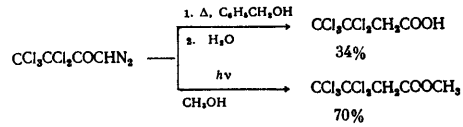
It is possible by using the classical method to effect the rearrangement of diazo-ketones under quite mild conditions, but the reaction products are then strongly contaminated by traces of colloidal silver or of silver salts. Moreover, the yields of the rearranged products are not always satisfactory[163,164], and in several cases, therefore, the thermal method of rearrangement is preferable. Thus an 85% yield of 2-1′-naphthylpropionanilide is obtained by thermolysis, whereas the yield of the acid itself on catalytic rearrangement of the same initial diazo-ketone is only 26%.[89] It is not at all possible under classical conditions to rearrange diazo-ketones obtained from *p*-anisoyl and *p*-toluoyl chlorides, whereas their thermolysis in benzyl alcohol permits the homologous acids to be isolated in yields of 76% and 79% respectively[89].

The photolytic method of effecting the rearrangement is the most widely applicable and the most convenient[93,94,115,165-172]. Whereas the yield of diphenylketen obtained by the thermal decomposition of azibenzil[73] is 77%, photolysis of the latter compound for 3 h enables a 92% yield of the keten to be isolated[93]. Irradiation of azibenzil in aqueous dioxan gives diphenylacetic acid[92,93,169] in excellent yield. If the illumination is conducted in ethanol, the ethyl ester is obtained. Weygand effected the photolysis of diazoacetone in the presence of *N*-methylaniline and ethanethiol respectively[173], and obtained a 77% yield of *N*-methylpropionanilide and a 67% yield of ethyl thiolopropionate:

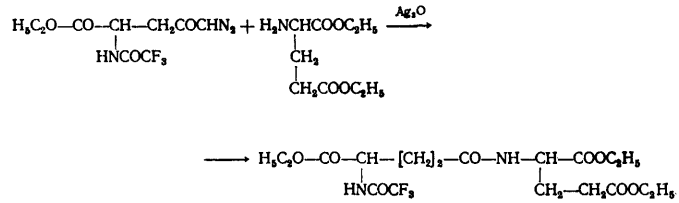


The photolytic method enables the Wolff rearrangement to be accomplished under the mildest conditions, and hence usually unaccompanied by any side-processes or resinification, which cannot be completely avoided in the catalytic or thermal decomposition of diazo-ketones.

It is especially important that the photolysis of diazo-ketones can often be successfully applied where the thermal and catalytic methods of rearrangement do not give positive results[4,174-180]. Thus 3,4,4-trichloro-1-diazobut-3-en-2-one $CCl_2{:}CClCOCHN_2$, because of its sensitivity to alkalis, does not rearrange under classical conditions, but can be converted into the corresponding acid by ultraviolet irradiation[175]. The great stability of 3,3,4,4,4-pentachloro-1-diazobutan-2-one makes rearrangement of this diazo-ketone impossible under classical conditions, but this can be achieved by thermolysis in benzyl alcohol in the presence of collidine at 150–190° [89] or by ultraviolet irradiation:



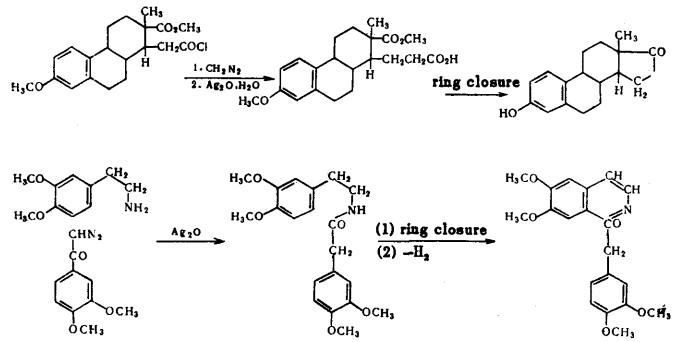
Mild reaction conditions (in photolysis or catalytic decomposition) make it possible to employ the Wolff rearrangement for the synthesis of complicated compounds containing functional groups, such as amino-acids and their derivatives[137-139,157,181], peptides, and polypeptides[5,135,136]. For example, the ethyl ester of δ-diazo-γ-oxo-*N*-trifluoroacetyl-L-norvaline in the presence of diethyl glutamate gives a good yield of triethyl *N*-trifluoroacetyl-γ-L-glutamyl-L-glutamate[134,182]:



An interesting example of the Wolff rearrangement is reported by Balenović[181], who succeeded in preparing α-methyl-β-alanine in 91% yield:

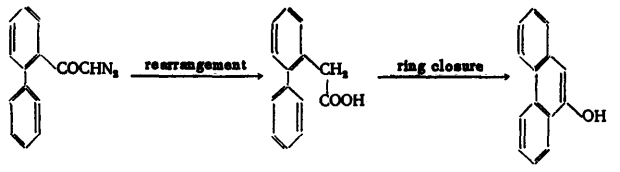
$$NH_2CH_2COCN_2CH_3 \rightarrow NH_2CH_2CH(CH_3)CONHC_6H_5 \rightarrow NH_2CH_2CH(CH_3)COOH.$$

In the work of this author the Wolff rearrangement is widely used for the conversion of α-amino-acids into β-amino-acids[5,157]. The rearrangement has been employed to obtain several intermediate products for the synthesis of natural substances, in isolated cases the natural substances themselves, e.g. oestrone, papaverine[183]:

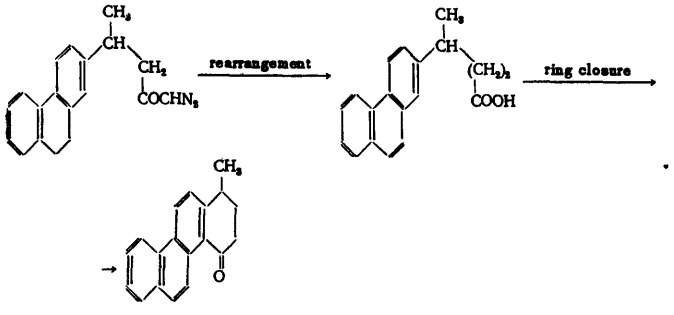


and several other related compounds[141,184]. It enables difficultly accesssible compounds to be prepared as well as compounds which cannot be obtained in other ways. Thus

the Wolff rearrangement constitutes one stage in the synthesis of 9-hydroxyphenanthrene[154]:



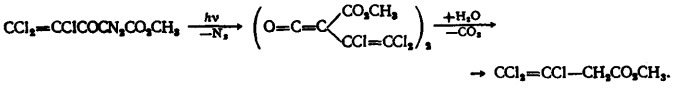
as also in the preparation of trimethoxyphenylacetic acid[185] and of 1,2,3,4-tetrahydro-1-methyl-4-oxochrysene[186]:



The Wolff rearrangement goes successfully also with diazo-ketones containing multiple bonds[122-125], the best results being obtained in a homogeneous medium, in the presence of silver benzoate and triethylamine. Wotiz[125], by using this method, isolated methyl non-7-ynoate in 80% yield, whereas under classical conditions the yield of this ester is 65%.[75]

Comparatively few α-diazo-ketones cannot undergo the Wolff rearrangement. They include perfluorinated diazo--ketones: at least two methylene groups must be present between a perfluorinated radical and the carbonyl group for the rearrangement to give a satisfactory yield[157,179,187,188]. Diazo-ketones obtained from completely fluorinated propionic, butyric, and valeric acids, for example, do not undergo the Wolff rearrangement, and the diazo-ketone $C_3F_7CH_2COCHN_2$ gives only a small quantity of the homologous acid, whereas the diazo-ketone $C_3F_7[CH_2]_2COCHN_2$ rearranges normally and in good yield. Nevertheless, the diazo-ketones obtained from trifluoroacetic and trichloroacetic acids has been shown[159] to undergo the Wolff rearrangement, although only the esters of the homologous acids are obtained from them in satisfactory yield, whereas production of the acids themselves, their amides, and their anilides is poor.

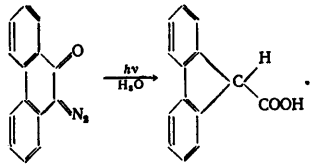
Ethyl trifluoro- and trichloro-acetylcarbenecarboxylates, which appear when trifluoro- and trichloro-α-diazoacetoacetic esters are illuminated, likewise do not undergo the Wolff rearrangement, probably owing to the strong electronegative effect of the trifluoromethyl and trichloromethyl groups[177]. However, recent work has shown[176] that the photolysis of the 4,5,5-trichloro-2-diazo-3-oxopent-4-enoic ester results in partial formation of the normal rearrangement products:



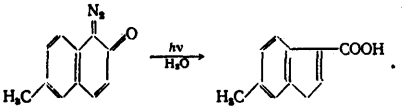
→ $CCl_2=CCl-CH_2CO_2CH_3$.

2. Wolff Rearrangement as a Method of Ring Contraction

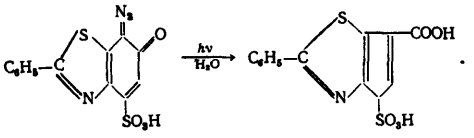
The Wolff rearrangement is of great value in the cyclic α-diazo-ketones series, when it involves ring contraction. The photochemical rearrangement of "quinone diazides" or "diazo-oxides" is a method of synthesising acids in the cyclopentadiene series[189-193]. Thus when phenanthrene--9,10-diazoquinone is illuminated in aqueous dioxan containing added acetic acid, fluorene-9-carboxylic acid is obtained in 80–88% yield[189]:



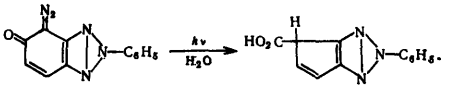
A 47% yield of 5-methylindene-1-carboxylic acid has been obtained by the photolysis of 6-methylnaphtha-1,2-diazoquinone[190]:



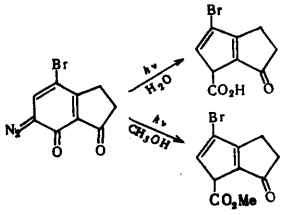
When 7-diazo-6,7-dihydro-6-oxo-2-phenylbenzothiazole-4-sulphonic acid is illuminated, the corresponding carboxylic acid is formed[190]:



4-Diazo-4,5-dihydro-5-oxo-2-phenylbenzotriazole gives 2-phenylcyclopentadienotriazole-4-carboxylic acid[191] in 43% yield:

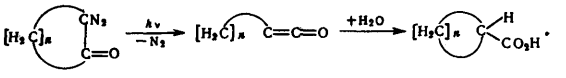


Horner and his coworkers have used the rearrangement of diazoquinones also to prepare pentalene derivatives[121]. They find that illumination of 4-bromo-6-diazo-6,7-dihydroindane-1,7-dione in dilute hydrochloric acid results in formation of the corresponding acid in 15% yield:



whereas exposure of the same compound in methanol to which concentrated hydrochloric acid has been added gives a 75% yield of the methyl ester of the acid.

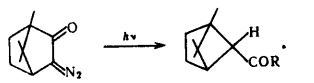
Alicyclic diazo-ketones on photolysis are converted into carboxylic acids with contraction of the ring[55,115,169]:



The tendency of diazo-ketones to undergo rearrangement is so great that rings are often formed which are

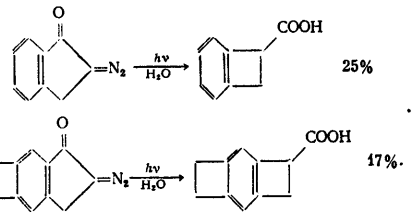
more strained than the original rings: five-membered from six-membered rings, and four-membered from five--membered rings[54,58,190,192-202]. Three cases have been reported in the pinane series in which the Wolff rearrangement did not take place[27]. Since, however, no indication was given of the reaction conditions, nothing can be said as to the reason for the absence of rearrangement in these cases.

The photolysis of diazocamphor[169] in aqueous medium gives a 76% yield of 1,6,6-trimethylbicyclo[2,1,1]hexane--5-carboxylic acid (R = OH):

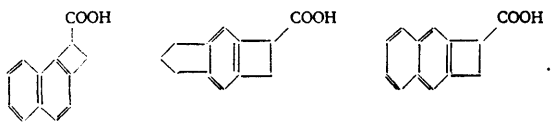


Irradiation of diazocamphor dissolved in ethanol, aniline, diethylamine, or dioxan containing hydrazine hydrate results in the formation of the ethyl ester, anilide, diethylamide, or hydrazide of this acid [R = OC_2H_5, NHC_6H_5, $N(C_2H_5)_2$, or $NHNH_2$ respectively].

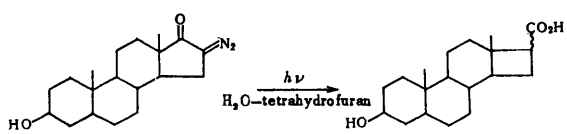
Horner and his coworkers applied the Wolff rearrangement to the preparation of cyclobutenobenzene derivatives, which for a long time had been regarded as unstable[115,194]:



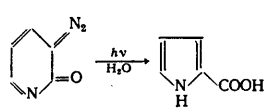
In spite of the low yields in individual cases, this reaction found wide application for the synthesis of complicated fused systems[55,194]:



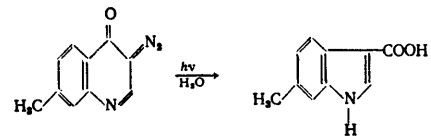
There are several interesting examples of ring contraction also among steroids[203-208] and triterpenes[63]. Thus illumination of 16-diazo-3β-hydroxyandrostan-17-one yields 3β-hydroxy-D-norandrostane-16-carboxylic acid[208]:



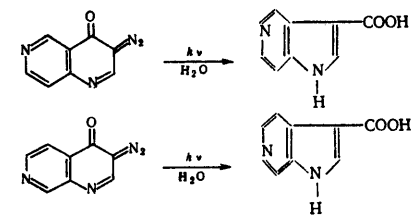
The Wolff rearrangement has been applied to heterocyclic α-diazo-ketones considerably less feequently. It was only in 1953 that Süs and his coworkers effected the Wolff rearrangement in certain nitrogen heterocycles of this type. Thus by the photolysis of 3-diazo-2,3-dihydro--2-oxopyridine they obtained pyrrole-2-carboxylic acid[190]:



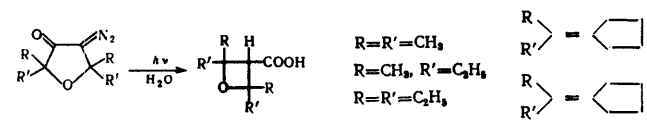
Using the same method Süs was able to synthesise several indolecarboxylic and azolopyridinecarboxylic acids[209,210]. Thus he isolated 6-methylindole-3-carboxylic acid in 80% yield[209]:



The photolysis of 3-diazo-3,4-dihydro-4-oxo-1,6(and 7)--diazanaphthalenes gives the corresponding 1,5(and 6)-diazaindene-3-carboxylic acids in ~ 50% yields[210]:



We have accomplished the conversion of tetrahydrofuran derivatives into oxetancarboxylic acids[117,211,212].



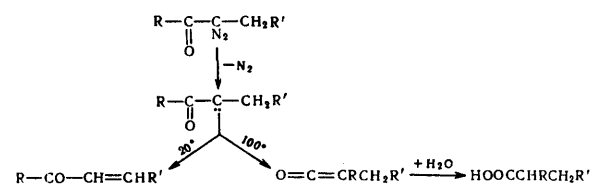
The reaction was conducted under classical conditions (in the presence of silver oxide), thermally, and photolytically. The best results were obtained by the photolysis of 2,2,5,5-tetra-alkyl-4-diazotetrahydro-3-oxofurans, the yields of the resulting 2,2,4,4-tetra-alkyloxetan-3-carboxylic acids being very high (60–97%), the reaction being simple to carry out, and no side-products being formed. This is the first example of the Wolff rearrangement among oxygen-containing heterocyclic α-diazo-ketones.

V. REACTIONS COMPETING WITH THE WOLFF REARRANGEMENT

Intramolecular rearrangement is not the only way in which the carbenone — the compound formed initially on detachment of nitrogen from a diazo-ketone — can be stabilised. The present Section discusses the chief transformations of α-diazo-ketones which compete with the Wolff rearrangement.

1. Hydrogen and Alkyl Migration

With diazo-ketones of the type $RCOCN_2CH_2R'$ rearrangement is accompanied by the migration of hydrogen, which results in the formation of an αβ-unsaturated ketone:



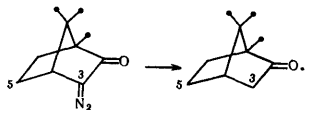
The relative proportions of the products depend on the reaction conditions. At room temperature the carbenone

is converted mainly into the $\alpha\beta$-unsaturated ketone. Thus on decomposing 3-diazo-4-phenylbutan-2-one in the presence of silver oxide, Franzen isolated 55% of 4-phenylbut--3-en-2-one[213]:

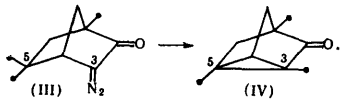
$$C_6H_5CH_2CN_2COCH_3 \longrightarrow C_6H_5CH{=}CHCOCH_3 + C_6H_5CH_2CH(CH_3){-}COOH.$$

At temperatures exceeding 100° the predominant reaction is rearrangement with formation of α-methyl-β-phenylpropionic acid. Franzen showed also that the reaction goes similarly under ultraviolet irradiation in the absence of a catalyst[213].

A new reaction of the same type — alkyl migration — has recently been discovered[77]. In contrast to photolysis, which gives the normal product of the Wolff rearrangement, heating diazocamphor in the presence of copper results in migration of a hydrogen atom† with formation of camphor[42]:



Compounds were therefore studied in which the $C_{(5)}$ position was occupied. Thus the diazo-ketone (III) was prepared from isofenchone, and its decomposition in the presence of copper bronze gave the ketone (IV) in 53% yield. In this case migration of a methyl group takes place, with formation of a $C_{(3)}-C_{(5)}$ bond:



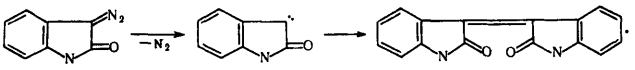
Hence in this instance *C*-alkylation competes successfully with the Wolff rearrangement.

2. Dimerisation and Trimerisation

As already mentioned, copper, like silver, accelerates the elimination of nitrogen from diazo-ketones, and is therefore sometimes used as a catalyst in the Wolff rearrangement. However, in the presence of copper catalysts rearrangement of the diazo-ketone is usually suppressed by dimerisation of the intermediate carbenone to a diacylethylene[78-86]. It has been established that predominantly unrearranged products are formed in the presence of copper[76], cuprous oxide[87], cupric oxide[82,215-218], copper chloride[87,219], and copper acetate or benzoate[87]. The copper catalysts are assumed[220] to stabilise the carbenone, whose rate of rearrangement into a keten is so strongly diminished that intermolecular interaction begins to predominate over intramolecular conversion. Thus when diazoacetophenone is heated in an inert solvent in the presence of cupric oxide, 1,4-diphenylbut-2-ene-1,4-dione is formed, to which Paal[221] has assigned the *trans*-configuration:

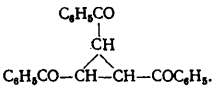
$$2C_6H_5COCHN_2 \xrightarrow{CuO} C_6H_5COCH{=}HCCOC_6H_5.$$

1,6-Diphenylhex-3-ene-2,5-dione $C_6H_5CH_2COCH{:}CHCOCH_2C_6H_5$, 1,2-distearoylethylene [octatriacont-19--ene-18,21-dione] $C_{17}H_{35}COCH{:}CHCOC_{17}H_{35}$, etc. have similarly been prepared from the corresponding diazo-ketones[78]. In some cases the dimerisation of carbenones occurs so readily in the presence of copper catalysts that this reaction is used as a method of synthesising symmetrical and even unsymmetrical unsaturated γ-diketones[79-85,241]. Isoindigo, for example, has been synthesised in this way[223]:



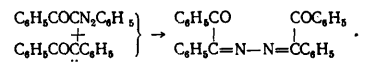
The course of the reaction is similar with 2-diazoindan--1-one[222].

In isolated cases[73,78] a more complicated intermolecular interaction of the intermediate carbenones — trimerisation — has been observed. Thus after boiling diazoacetophenone in isopentyl ether, Grundmann was able to isolate a very small quantity of *cis*-1,2,3-tribenzoylcyclopropane[78]

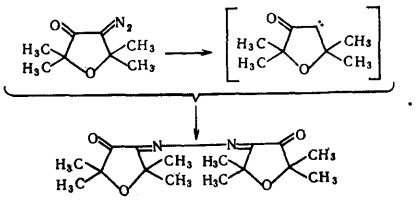


3. Formation of Ketazines

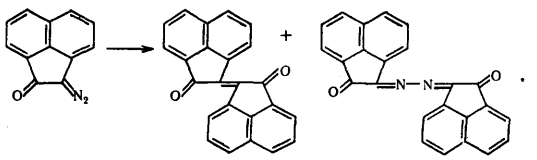
In the thermal decomposition of diazo-ketones — with or without a catalyst present — a further type of intermolecular reaction is possible, the intermediate carbenone interacting with the original diazo-compound[224-227]. Thus the decomposition of azibenzil in the presence of cupric oxide results in the formation of benzil monoazine[78]:



We have observed a similar course of reaction in the catalytic thermal decomposition of 4-diazotetrahydro--2,2,5,5-tetramethyl-3-oxofuran[212]:



The thermolysis of 2-diazoacenaphthen-1-one[228] results in a mixture of two products — biacenaphthenylidenedione and acenaphthenequinone monoazine:



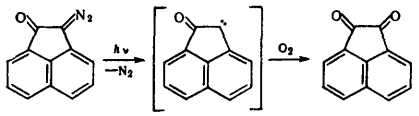
The pyrolysis of 3-diazo-1-methyl-2-oxoindoline has also led to isolation of the corresponding ethylenic derivative and the azine — 1,1′-dimethylisoindigo and 1,1′-dimethylisatin azine[229].

4. Oxidation of Intermediate Carbenones

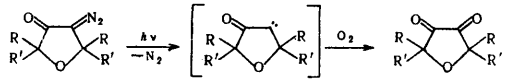
Cases of the oxidation of carbenes have been described in the literature. Diphenyldiazomethane when exposed to light, for example, adds on oxygen and is converted into

† There are other examples in which photolysis and thermolysis of diazo-ketones result in different reaction products[214] (see also Subsection 5, below).

benzophenone[224]. An analogous process, which completely suppresses the Wolff rearrangement, obviously occurs with diazoacenaphthenone[115], where only the corresponding α-diketone can be isolated after illumination:



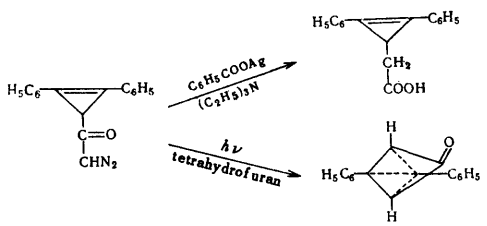
We have also observed the formation of small quantities of 2,2,5,5-tetra-alkyltetrahydrofuran-3,4-diones in the rearrangement of 2,2,5,5-tetra-alkyl-4-diazotetrahydrofuran--3-ones[212]:



where R = R′ = CH_3 and R = CH_3, R′ = C_2H_5.

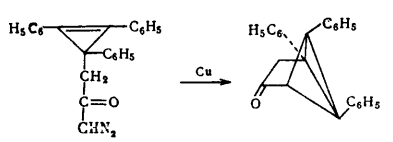
5. Intramolecular Addition of Carbenones at a Double Bond

An unusual result has been recorded in recent papers by Masamune[230,231], who has studied the rearrangement of diazomethyl 2,3-diphenylcyclopropyl ketone. He found that heating this compound with silver benzoate in triethylamine goes normally with a good yield of the methyl ester of the homologous acid. However, photolysis of the same diazo-ketone in tetrahydrofuran results in formation of a ketone belonging to the tricyclo[1,1,1,$0^{4,5}$]pentane system:



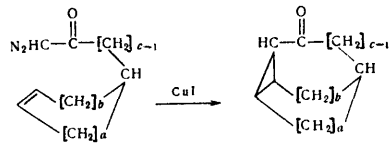
Hence in this case the α-ketocarbene formed on ultraviolet irradiation of the diazo-ketone exhibits a greater tendency to intramolecular addition at the double bond[3,4,232-235] than to rearrangement.

A similar type of reaction has been observed also by Small[236] and by several other workers[237-240]. Thus boiling 1-diazo-3-triphenylcycloprop-2′-enylpropan-2-one in benzene in the presence of copper powder results in a 57% yield of 4,5,6-triphenyltricyclo[2,1,1,$0^{5,6}$]hexan-2-one:



In the above examples the intramolecular addition of the carbenone at the double bond is obviously governed by the structural peculiarities of the initial diazo-ketones — by the presence of a nucleophilic double bond in the diazo--ketone molecule, and also of a strained unsaturated three--membered ring, which disappears as a result of the reaction.

The catalytic decomposition of monocyclic diazo-ketones containing a double bond in the ring has been used by Doering for the synthesis of tricyclic systems[239]:



(where a = 0–4, b = 0–2, and c = 1 or 2), which he obtained in preparative yields. Other workers have carried out similar transformations[242,243].

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Leningrad State University

U.D.C. 547.39

CHEMISTRY OF NATURAL ALIPHATIC ACIDS CONTAINING A CONJUGATED SYSTEM OF DOUBLE BONDS

V.D. Solodovnik

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1. INTRODUCTION

Until recently only a very small number of aliphatic acids containing a conjugated system of double bonds had been found in Nature. These acids had been isolated in individual cases from plant lipids, and were regarded in oil and fat chemistry as fairly rare exceptions. The view was even expressed that they might have been formed in the course of isolation, by the isomerisation of unconjugated polyenoic acids. However, several new representatives of this class of compounds have been discovered in recent years, and aliphatic acids containing conjugated double bonds have been shown to be present in the lipids from plants of a great variety of families and species. Sixteen natural conjugated polyenoic aliphatic acids are now known, and the number of natural sources for acids of this type is continually being extended.

Conjugated polyenoic acids form the basis of many long-established film-forming materials. The paint and varnish industry has hitherto made widespread using of drying oils, in which conjugated polyenoic acids either are present in the sodium form (tung oil) or have been formed, as a result of preliminary treatment, from unconjugated polyenoic acids present in linseed or other vegetable oil. In contrast to oils containing unconjugated polyenoic acids, the triglycerides of conjugated acids give valuable varnishes, which dry more rapidly and are more stable to the action of moisture and alkalis.

2. GENERAL PROPERTIES AND METHODS OF ESTABLISHING STRUCTURE

The C_{18} conjugated polyenoic acids most frequently encountered in Nature are colourless crystalline solids. Naturally occurring acids of this type containing a smaller number of carbon atoms in the chain melt below room temperature. They all dissolve well in polar organic solvents, and less well in non-polar solvents.

Polyenoic acids containing *cis*-ethylenic bonds readily isomerise into all-*trans*-isomers under the influence of light and especially in the presence of traces of iodine, sulphur, nitrogen dioxide, and other catalysts.

As a result of the presence of a chromophoric group, conjugated polyenoic acids are able to absorb ultraviolet radiation. Examination of the ultraviolet spectra of stereoisomeric dienoic acids has shown that *trans-trans*-isomers absorb at shorter wavelengths than do *cis-trans*- and *cis-cis*-isomers, the intensity of the absorption maxima diminishing in this sequence. Thus the ultraviolet spectra of the stereoisomeric octadeca-9,11- and -10,12-dienoic acids contain a single maximum at 230, 232, and 234 nm respectively for the *trans-trans*-, *trans-cis*-, and *cis-cis*-isomers[1]. The variation in the position of the absorption maximum and in its intensity is less marked in the spectra of the deca-2,4-dienoic acids, owing to conjugation of the diene group with the carboxyl, but is sufficient to distinguish them[2]. Variations in the ultraviolet spectra are still more marked among the stereoisomers of conjugated trienoic acids, since their spectra contain three absorption maxima (Table 1).

Infrared spectroscopy has an important place in establishing the structure of conjugated polyenoic aliphatic acids. Alkenes of the type RCH:CHR′ are characterised by an intense band at 950–1100 cm^{-1}, due to deformation vibrations

TABLE 1. Ultraviolet spectra of C_{18} conjugated trienoic acids (λ_{max}, nm).

Conjugation	Positions 8, 10, 12	Positions 9, 11, 13	Ref.
cis-trans-cis	265, 275, 287	264, 274, 285	3, 4, 5
		265, 275, 287	5
cis-cis-trans	not known	(264), 271, (279)*	4
cis-trans-trans	261, 271, 232	261, 271, 281	6, 3
trans-trans-cis	262, 272, 283	262, 272, 283	7, 8
trans-trans-trans	259, 269, 280	260, 269, 281	7, 6
	259, 269, 279	259, 268, 279	3, 5

* Values in parentheses relate to an unpurified specimen.