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PYRAZOLIDINE-3,5-DIONES, THEIR SYNTHESIS AND PHARMACOLOGICAL IMPORTANCE

A.M. Khaletskii and B.L. Moldaver

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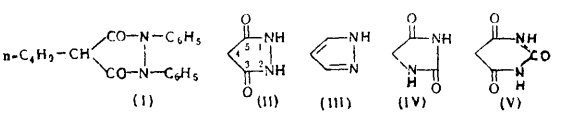
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I. INTRODUCTION

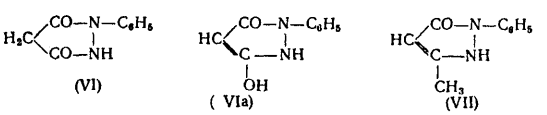
The discovery of the valuable therapeutic properties of 4-n-butyl-1,2-diphenylpyrazolidine-3,5-dione[1] (Butazolidine, Phenylbutazone, Butadione†) (I) promoted the development of the chemistry of this group of compounds. Thus, whereas a total of about 25 papers appeared in the 60 years after the synthesis of the first pyrazolidine-3,5-diones[2], in the last decade, and mainly during the last five years, no fewer than 300 papers and patents dealing with this group of substances have been published, not counting the hundreds of papers connected with the study of Butadione itself.

At the present time various methods of synthesising pyrazolidine-3,5-diones have been developed and many of their properties have been studied but these results are dispersed in numerous articles and it is difficult for the research worker to cover them. Much material present in dissertations (*e.g.* that of Têng[3]) is not accessible and the section on pyrazolidine-3,5-diones in Jacobs' article in the recently issued Volume V of the Collection "Heterocyclic Compounds"[4] is very short and to some extent out-of-date, because only references up to 1954 are included. The present review is an attempt to survey the published material on the chemistry of pyrazolidine-3,5-diones and their applications.



(I) (II) (III) (IV) (V)

Pyrazolidine-3,5-dione (II) is the 3,5-dioxo-derivative of completely hydrogenated pyrazole (III). It is isomeric with hydantoin (IV) and is structurally related to barbituric acid (V), and also to pyrazolones.

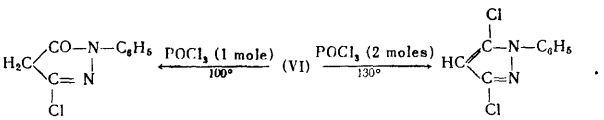


(VI) (VIa) (VII)

Thus, the enol form (VIa) of 1-phenylpyrazolidine-3,5-dione (VI) differs from 3-methyl-1-phenylpyrazol-5-one (VII)

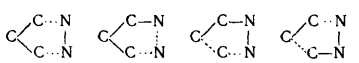
† Trivial name used in USSR (Ed. of Translation).

only in having a hydroxyl group in place of the methyl. The conversion of pyrazolidine-3,5-diones to pyrazolones and pyrazoles was described in 1898.[5]



II. METHODS OF PREPARATION

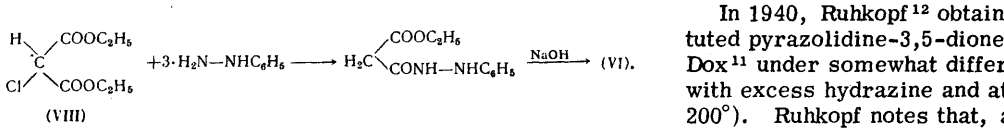
The many methods of synthesising pyrazolidine-3,5--diones can be divided, according to the types of bond being formed in the reaction (C–N, N–N, C–C, and their combinations), into the following four groups‡:



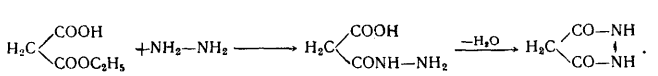
In addition, the preparation of pyrazolidine-3,5-diones from 3-imino-5-oxopyrazolidines forms a fifth group.

1. Formation of Two C...N Bonds. Preparation from Derivatives of Malonic Acid and Hydrazine

In 1891 Burmeister and Michaelis[2] described the preparation of 1-phenylpyrazolidine-3,5-dione (VI) from diethyl chloromalonate (VIII) and phenylhydrazine:

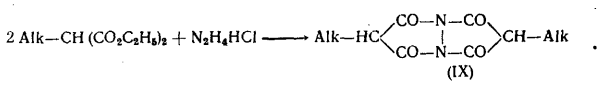


1-*p*-Tolylpyrazolidine-3,5-dione was prepared similarly[6]. This method was not used further because the use of chloromalonic ester (VIII) was found to be not essential. Rothenburg[7] prepared the unsubstituted pyrazolidine-3,5--dione (III) by heating monoethyl malonate with hydrazine hydrate; water is lost and the ring is closed on distilling:

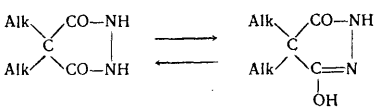


This is the only reference to the preparation of (III). Rothenburg's results have been questioned by other investigators[8]. Syntheses of pyrazolidinediones without condensing agents are now rarely encountered[9].

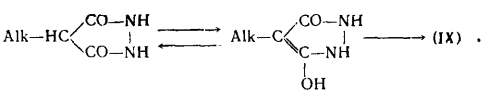
Condensation in the presence of alkaline agents was found more convenient. Conrad and Zart[10] obtained 1-mono- and 1,2,4-tri-substituted pyrazolidine-3,5-diones in satisfactory yields using sodium metal, its amide, or alkoxide and carrying out the reaction at 110°–120° for 12 h. This method has found wide application in view of the ready availability of substituted malonic esters. Dox showed[11] in 1932 that it can be used to prepare 4,4-dialkylpyrazolidine-3,5-diones. Under the same conditions monoalkyl malonates, in contrast to dialkyl malonates, invariably gave 1,3,5,7-tetraoxopyrazo[1,2-*a*]pyrazoles (IX) with hydrazine:



The author considered a possible reason for the different behaviour of mono- and di-substituted malonates to be the presence in 4,4-disubstituted pyrazolidine-3,5-diones of lactim-lactam tautomerism, which makes further condensation with a second dialkyl malonate molecule at the nitrogen impossible:

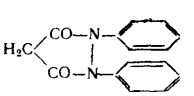


Keto-enol tautomerism in the monoalkylpyrazolidine--3,5-diones does not prevent formation of a compound of type (IX):



Further work, which shows that the hydrogen atom at C_4 is more mobile than that at the nitrogen, supports this hypothesis.

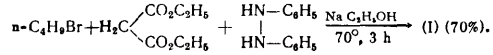
In 1940, Ruhkopf[12] obtained a number of 4,4-disubstituted pyrazolidine-3,5-diones, which had been described by Dox[11] under somewhat different reaction conditions, *viz.* with excess hydrazine and at a higher temperature (180°–200°). Ruhkopf notes that, as the carbon chain of the substituent in the malonic ester lengthens, the tendency to ring-closure is reduced; the same is observed when the hydrazine molecule is "enlarged" by various substituents. For example, he could not achieve ring-closure of ethyl phenyl malonate with phenylhydrazine. He also showed that Conrad and Zart's method is applicable to the preparation of 1,2-diphenylpyrazolidine-3,5-dione (X). 1,2,4-Trisubstituted pyrazolidine-3,5-diones were synthesised by this method in 1950 by Stenzl[13]. The synthesis of a number of 4-monosubstituted 1,2-diphenyl-3,5-dioxopyrazolidines has also been described in patents[14,15]. The last 15 years has been a period of intensive research on pyrazolidine-3,5--diones and particularly on the 1,2-diphenyl derivatives. In 1953 Büchi and coworkers[16] noted the great possibilities of Conrad and Zart's method for the preparation of mono-, di-, and tri-substituted pyrazolidine-3,5-diones. At the same time, they considered the preparation of 1,2,4,4-tetrasubstituted pyrazolidine-3,5-diones by this method to be impossible. The work of Khaletskii, Pesin, and Têng[3,17] showed that, although the tetrasubstituted pyrazolidine-3,5--diones are actually unstable in an alkaline medium, they can all be isolated in 2–3% yield. There are also indications in patents[18] that the 1,2,4,4-tetrasubstituted compounds can be prepared by this method but the yields are not quoted.



(X)

‡ The full lines signify bonds in the pyrazolidine-3,5-dione skeleton which are already present and the dotted lines those being formed in the reaction.

In the last decade, many variations of the method described have been published, differing in the solvents used, the reaction temperature, and condensing agents. Sodium butoxide[19-21] and piperidine[22] have been used as condensing agents, and ethanol or xylene, butanol[20,23], mineral oil[24], cyclohexanol[25,26], polyethyleneglycol[27], etc., as solvents. A fortunate choice of solvent often affects the product yield markedly[28]. Whereas in older work the reaction was often carried out at high temperatures (up to 200°), recently lower temperatures (100°–120° and even 85°[18]) have usually been used. The combining of condensation with alkylation has been suggested[29,30].



The yield is raised by carrying out the reaction in a nitrogen atmosphere[31].

In 1907 Michaelis and Schenk[32] achieved the condensation of a number of mono- and di-substituted malonic acids with monosubstituted hydrazines in the presence of phosphorus trichloride. In subsequent work[33] they described the preparation of 1,4-disubstituted and 1,2,4,4-tetrasubstituted pyrazolidine-3,5-diones by the same method; the applicability of the method was confirmed in 1942,[34] but it is comparatively rarely used now. The preparation of 1,4-diphenylpyrazolidine-3,5-dione and 2-alkyl-1,4-diphenylpyrazolidine-3,5-diones has been described[35,36]. Substituted malonyl chlorides are much more frequently used. Rothenburg[7] was the first to report the use of malonyl chloride as a very active product for the formation of pyrazolidine-3,5-diones. Two years later, the preparation of 1-tolylpyrazolidine-3,5-dione in low yield from malonyl chloride and *p*-tolylhydrazine was described[6]. 4,4-Diethylpyrazolidine-3,5-dione was synthesised from hydrazine and diethylmalonyl chloride by the same method[37]. The method was studied in greater detail by Kaufmann[38], who used dimethylaniline to combine with the acid produced and obtained a number of 1,2,4,4-tetrasubstituted pyrazolidine-3,5-diones in yields up to 60%.

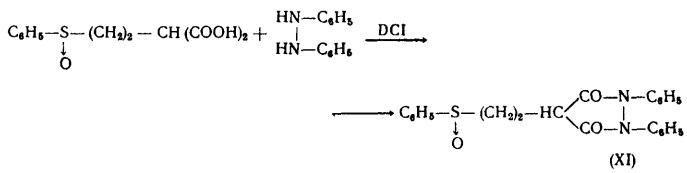
Tsumaki[39] used the same method, but without condensing agents, to obtain for the first time 1,2-diphenylpyrazolidine-3,5-dione (X) in 30% yield.

This method has been used repeatedly in recent years to prepare various pyrazolidine-3,5-diones. The reaction is usually carried out at a low temperature (0°) in a solvent inert with respect to the acyl chloride (benzene, ether) in the presence of an organic tertiary base (pyridine, dimethylaniline)[15,40,41]. By thus maintaining mild condensation conditions, tetrasubstituted pyrazolidine-3,5-diones containing bromine at C_4[42-44] and also an acetyl derivative of *p*-hydroxyphenylbutadione[45,46] were prepared. Good yields (80–90%) were obtained by Linnel and Khalifa[47] in the synthesis of 4-monoalkyl-1,2-diarylpyrazolidine-3,5-diones containing substituents such as $-NO_2$, $-NHCOCH_3$, $-CO_2H$, and $-OCOCH_3$ in the *para*-position of the benzene rings, by heating the hydrazo-compound with a small excess of the acyl chloride in benzene for 3 h at 70°–80° and then distilling off the benzene and excess acyl chloride. Lower yields (50–70%) are observed when the reaction is carried out in the presence of acetic anhydride (as solvent) in a nitrogen atmosphere. The preparation of 4-butyl-1-phenylpyrazolidine-3,5-dione from butylmalonyl dichloride and phenylhydrazine has also been described[48].

The above method has been widely used to synthesise a large number of *N*-substituted pyrazolidine-3,5-diones[49-52].

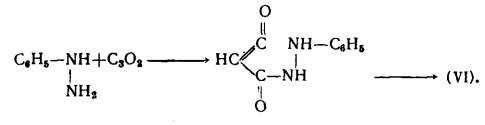
To prepare Butadione, butylmalonic anhydride is condensed with hydrazobenzene in the presence of pyridine or triethylamine in ether or chlorine-containing hydrocarbons; the yield of Butadione reaches 93%.[53]

The use of dicyclohexylcarbodiimide (DCI) for preparing pyrazolidine-3,5-diones with optically active substituents is of great interest. By this means Pfister[36] obtained two optically active forms of 1,2-diphenyl-4-(2-phenylsulphinylethyl)pyrazolidine-3,5-dione (XI):

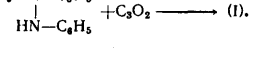


(XI)

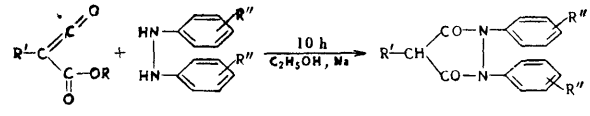
Van Alphen showed[54] in 1924 that 1-phenylpyrazolidine-3,5-dione (VI) is formed in the reaction of equivalent quantities of carbon suboxide and phenylhydrazine in ether. The reaction occurs in two stages:



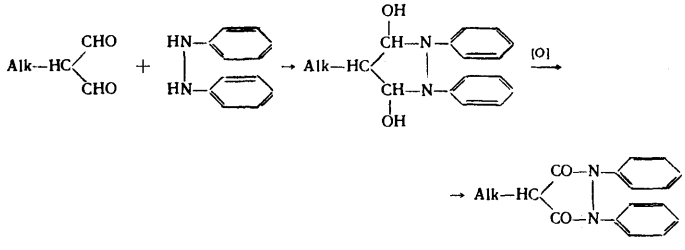
Excess phenylhydrazine leads to formation of by-products. Tsumaki[39] obtained 1,2-diphenylpyrazolidine-3,5-dione (X) in this way. The preparation of pyrazolidine-3,5-diones using carbon suboxide and hydrazine, its alkyl, cycloalkyl, aryl, and arylalkyl derivatives, is described in patents[55,56]: the reaction is carried out at -2° in an anhydrous inert solvent (xylene). Of trisubstituted hydrazines, only those with at least one alkyl radical with not more than four carbon atoms are suitable. For example, Butadione is obtained in 85% yield by this method:



When derivatives of keten are used it is necessary to heat to 110° in the presence of sodium metal[57].

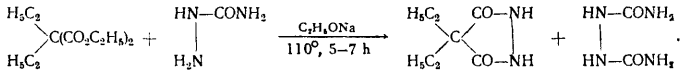


Malonyldialdehyde can also be used to synthesise pyrazolidine-3,5-diones[56]:

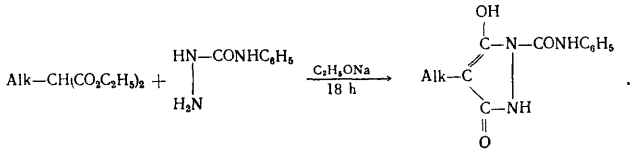


Many hydrazo-compounds are used in the reactions described: hydrazine, mono- and di-substituted alkyl-, aryl-, arylalkyl-, pyridyl-, cycloalkyl-, naphthyl-, and other

hydrazines. Dox showed[11] that a by-product of the reaction of disubstituted malonic esters with semicarbazide is hydrazodicarbonamide:

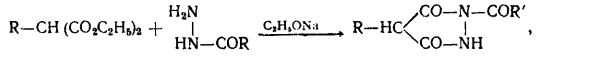


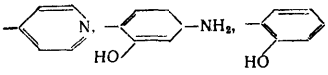
The reaction of monoalkylmalonic esters with 4-phenylsemicarbazide takes place differently[58]:



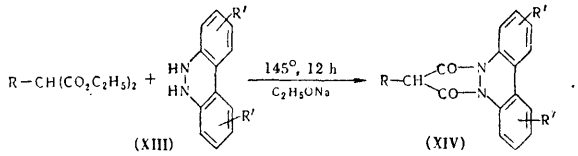
Semicarbazides, and thiosemicarbazides and di(ethoxycarbonyl)hydrazine, also react with malonyl dichloride and its derivatives to form pyrazolidine-3,5-diones in good yields[59-61].

Condensation of the hydrazides of a number of aromatic and heterocyclic acids with esters of monoalkylmalonic acids in the presence of sodium ethoxide occurs with satisfactory yields[62]:



where R = H, C_2H_5, C_4H_9; R' = .

The preparation of derivatives of *NN'*-malonyldihydrobenzo[*c*]cinnoline (XIV) by the usual methods from 5,6-dihydrobenzo[*c*]cinnoline (XIII) is reported in many patents[63-67]:



The use of *N*-mono- and *NN*-di-acetylated derivatives of hydrazobenzene leads to higher yields[68].

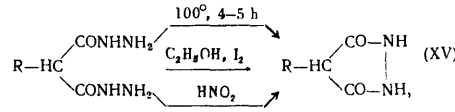
The use of azo-compounds is apparently very promising[69-71]. Thus, Butadione is obtained in 90% yield from organometallic compounds of azobenzene and butylmalonyl dichloride.

The substituents in the malonic acid (or its ester) which are used in reactions of this type are very various. Substances used include esters of numerous alkylmalonic acids[72] with up to 18 carbon atoms in the chain, and of straight chain and branched chain, arylalkyl-, and alkenyl--malonic acids, and also those with bicyclic[73,74] and heterocyclic radical substituents[75,76]. Many substituents containing a sulphur, oxygen, or nitrogen atom[9,75,77-79], an ester group[80], a shielded hydroxy-group[81], etc., in the side chain are used.

The effect of substituents in the molecule of the esters of monosubstituted alkylmalonic acids on their condensation with *o*-, *m*-, and *p*-chlorophenylhydrazines is of interest. The latter takes place, according to Gagnon's results[82], only if there are more than three carbon atoms in the substituent. To achieve condensation of esters of unsubstituted or methyl-, ethyl-, or propyl-malonic acids, they must be fused with the hydrazines at 165° and heated until the alcohol is distilled off completely.

2. Formation of an N...N Bond. Preparation from Dihydrazides and Dianilides§

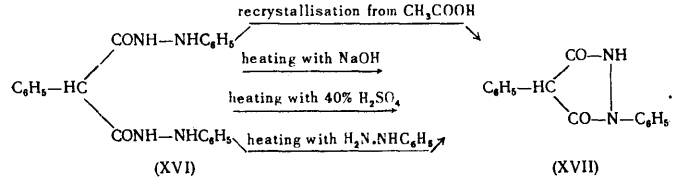
In 1916 Curtius described[83] the conversion of some 4-monosubstituted malonhydrazides into 4-monosubstituted pyrazolidine-3,5-diones (XV):



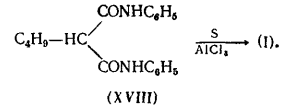
where R = $C_6H_5CH_2$, CH_3, C_6H_4, CH_2.

In subsequent investigations Curtius[84] noted that analogous compounds are formed as by-products.

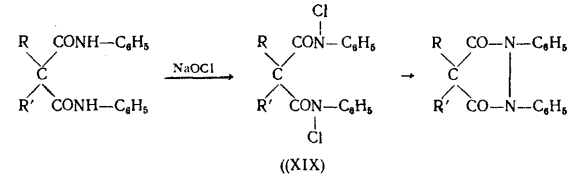
No other ways of preparing compounds of type (XV) have been described. The bisphenylhydrazide of phenylmalonic acid (XVI) behaves similarly:



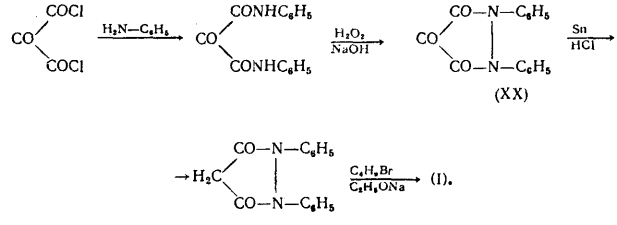
Diamides are the starting materials in some original methods of preparing pyrazolidine-3,5-diones. According to a patent[85], Butadione (I) is formed by treating the dianilide of butylmalonic acid (XVIII) with sulphur and aluminium chloride in dry benzene:



In another patent, the reaction of the dianilide of a disubstituted malonic acid with hypochlorite or chloramine, followed by catalytic dehalogenation of the intermediate *NN'*-dichloro-derivative (XIX) and ring-closure, is described[86]:



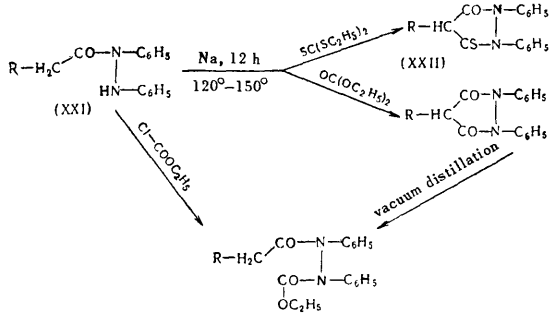
Butadione is also obtained *via* 1,2-diphenylpyrazolidine--3,4,5-trione (XX), by the following scheme[87]:



§ In some of the reactions described in this section it is unlikely that an N . . . N bond is formed (Ed. of Translation).

3. Formation of C...C...N Bonds. Preparation from Phenylhydrazides of Monobasic Carboxylic Acids

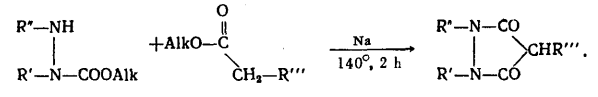
In 1957 Hallman reported[88-91] that pyrazolidine-3,5--diones are formed by the condensation of the *NN'*-diphenylhydrazides of carboxylic acids (XXI), which are easily obtained in good yields from hydrazobenzene and the acyl chloride, with diethyl carbonate or ethyl chlorocarbonate in the presence of alkaline agents. 1,2-Diphenyl-5-thiopyrazolid-3-ones (XXII) are formed when diethyl trithiocarbonate is used:



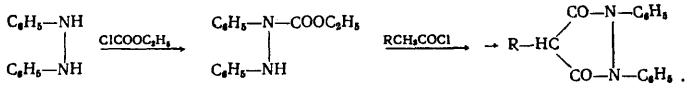
Similar methods are described in a number of patents[92].

4. Formation of C...C and C...N Bonds. Preparation by Condensing *N*-Carboxyhydrazines with Esters of Fatty Acids

The method is described in a Hungarian patent[93]:

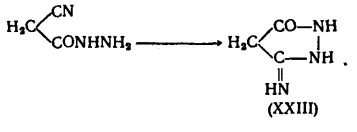


The following synthesis described in work mentioned above[88] occurs by the same scheme:

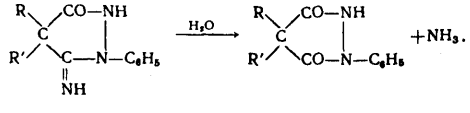


5. Preparation from 3-Iminopyrazolid-5-ones

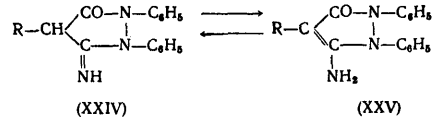
3-Iminopyrazolid-5-ones were first prepared from cyanoacetic ester and phenylhydrazine in the presence of sodium[10]. Unsubstituted 3-iminopyrazolid-5-one (XXIII) is obtained by treating cyanoacetylhydrazine with a 40% solution of sodium hydroxide[94]:



Syntheses of these compounds and study of their structure, tautomerism, and conversion into pyrazolidine-3,5--diones have been described in a number of papers[95-104]. The conversion takes place when they are hydrolysed by alkalis or acids:



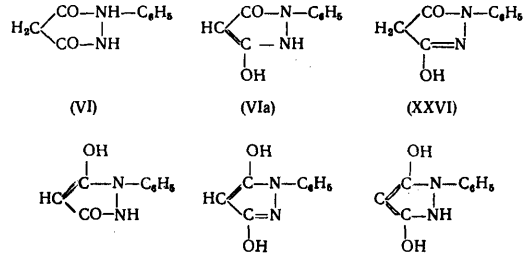
A number of authors, for example Stenzl[13], have demonstrated the existence of tautomerism between 3-iminopyrazolid-5-ones and 3-amino-Δ^3-pyrazolin-5-ones (XXV):



Study of the hydrolysis of 3-iminopyrazolid-5-ones[13] showed that, in contrast to compounds disubstituted or unsubstituted at the 4-position, compounds of type (XXIV) are only hydrolysed with difficulty. This can be explained by the stability of the tautomeric form (XXV).

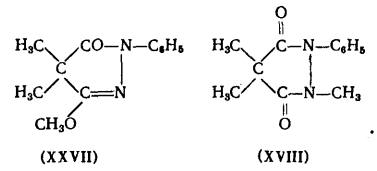
III. TAUTOMERISM IN THE PYRAZOLIDINE-3,5-DIONE SERIES

The existence of a number of tautomeric forms of pyrazolidine-3,5-diones is possible. Even for the first compound of the series which was obtained, 1-phenylpyrazolidine-3,5-dione (VI), Burmeister and Michaelis[2,105] were compelled to consider which of the possible structures should be ascribed to it:



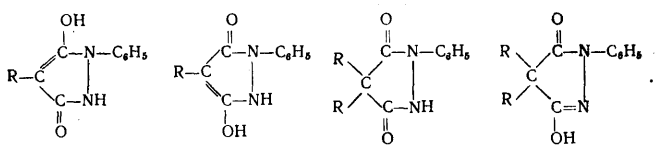
From the ease with which the substance reacts with aldehydes and ketones the presence of a methylene group in the molecule was suggested, and therefore formula (XXVI) was adopted. To confirm this the reaction of compound (XVI) with phosphoryl chloride and methyl iodide was studied. The *O*-methyl ether structure (XXVII) was ascribed to the methylation product.

Later, however, a substance identical with the methylated product (XXVII) was obtained in the condensation of *N*-methyl-*N'*-phenylhydrazine acetate with dimethylmalonic acid. These results[33] proved that the initial substance (VI) and its methylation product are 3,5-dioxo-compounds, (VI) and (XXVIII):



Thus, confirmation was already obtained of the existence of the diketo-form of pyrazolidine-3,5-diones early in their study, but the existence of enol forms was also indicated[7] by the formation by these compounds of salts with only one equivalent of metal and by the coloration with $FeCl_3$.

The use of ultraviolet and infrared spectroscopy permitted a deeper study of the tautomerism. By studying the ultraviolet spectra of 1,4-disubstituted pyrazolidine-3,5-diones Gagnon and coworkers[106] established the presence of two tautomeric forms (XXIX) and (XXX):



(XXIX) (XXX) (XXXI) (XXXII)

They also concluded, from the ultraviolet spectra and chemical properties of 1,4,4-trisubstituted pyrazolidine--3,5-diones, that these are present in neutral and acidic solutions as the diketo-form (XXXI), but in alkaline solutions as the lactim (XXXII). These results were subsequently confirmed[58,82]. It was also shown that *o*-, *m*-, and *p*-chloro-1-phenyl-4-substituted pyrazolidine-3,5--diones have identical ultraviolet spectra.

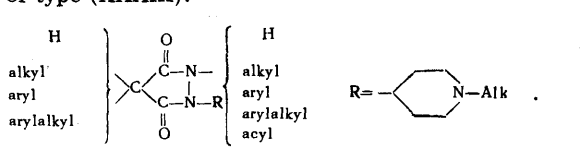
As a result of much research[96-102], begun in 1947, the relation between the position of the double bond in the tautomeric forms of 4-monosubstituted pyrazolidine-3,5-diones and the wavelengths, and also intensities, of the absorption bands was established.

The ultraviolet spectra of 1,2-diphenylpyrazolidine-3,5--diones were found to be similar to those of *N*-monosubstituted compounds[107-109].

Study of the infrared spectra of 4-mono- and 4,4-di--alkyl-1-phenylpyrazolidine-3,5-diones[82] also confirmed the existence of several tautomeric forms. A band at 7.7 μ was found[107,109-111] to be very characteristic of pyrazolidine-3,5-diones; this, together with bands close to 5.7 and 5.8 μ, which are characteristic of the carbonyl groups, is evidence of the presence of a pyrazolidine-3,5-dione ring. Similar results were obtained by Hammond *et al.*[109] for 4-alkoxy-1,2-diphenylpyrazolidine-3,5-diones; they isolated both tautomeric forms of these substances.

From a study of many 4-monosubstituted 1,2-diphenylpyrazolidine-3,5-diones, Girod[107] concluded that the majority of them exist in the diketo-form in solution and in the crystalline state. Some of these compounds are partially enolised in solution and a compound such as 1,2-diphenyl-4--(phenylthioethyl)pyrazolidine-3,5-dione exists in the enol form even in the crystalline state.

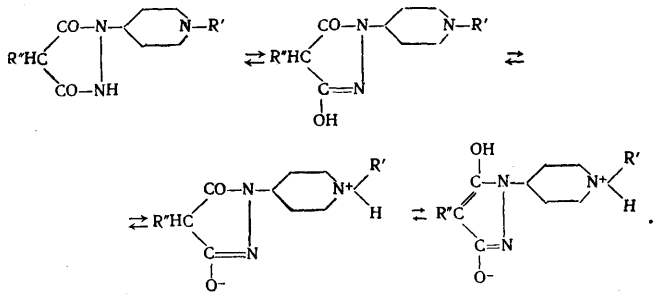
Ideas as to the tautomeric relationships in a number of pyrazolidine-3,5-diones were extended by studying compounds of type (XXXIII):[49,50,112-117]



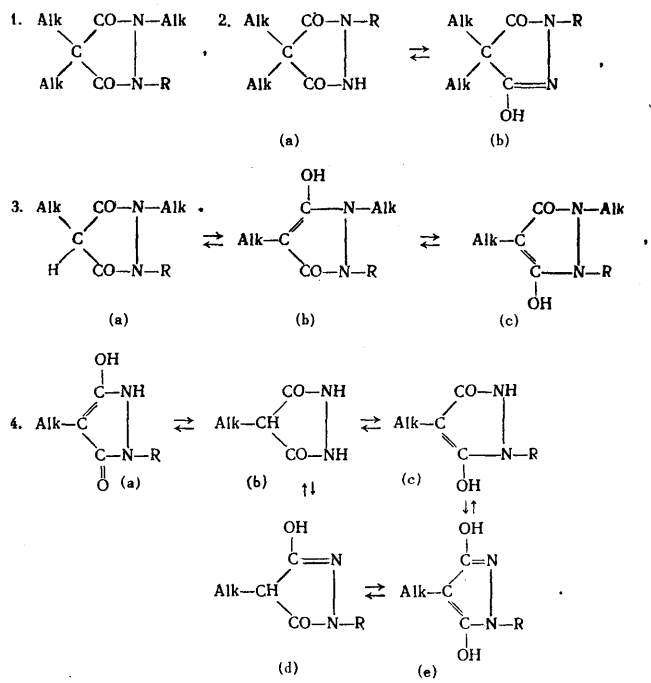
(XXXIII)

The relationships between the tautomeric forms in the series of these compounds are complicated.

Pyrazolidine-3,5-diones are acidic compounds, especially their 4-monosubstituted derivatives[106,107]. Thus, p*K* for Butadione corresponds to the acidity of aliphatic carboxylic acids. The presence in the molecule, therefore, of the basic nitrogen atom and the acidic enol or iminol hydroxyl leads to the formation of bipolar ions. For this reason the formation of iminol-enol, *i.e.* dihydroxypyrazole, tautomeric forms become possible in alkaline solutions:



Compounds of type (XXXIII) can be divided into four groups¶:

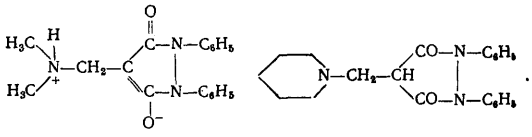


It was found that compounds of group 1 are in the diketo--form in aqueous solutions and in the solid state. Compounds of group 2 are in the iminol form (2b) in aqueous solutions. In chloroform both forms (2a) and (2b) are present, but in the solid state only the iminol form (2b). In acidic solutions and in weakly polar solvents compounds of group 3 are in the diketo-form (3a) but in neutral aqueous and in alkaline solutions they are in the enol form (3b) and (3c). In polar solvents compounds of group 4 are inclined more towards formation of the iminol (4d) and iminol-enol (4e) forms, which are stabilised by a basic substituent R, than to the enols (4a) and (4c), but in a weakly polar solvent (chloroform) two forms (4a) and (4d) are present.

Analogous tautomeric relations are characteristic of 4-amino-, 4-alkylamino-, and 4-aminoalkyl-pyrazolidine--3,5-diones[109]. Some peculiarities of their chemical properties are accounted for by this tautomerism; for example, compound (XXXIV) does not form alkaline salts although a reduction in the basicity of the nitrogen atom in

¶ The bipolar ions corresponding to these tautomeric forms are not indicated.

the side chain, for example in compound (XXXV), allows such a salt to be obtained[110]. High melting points are typical of all these compounds:

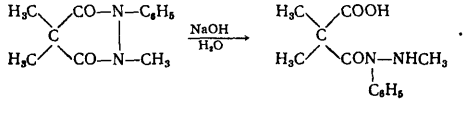


(XXXIV) (XXXV)

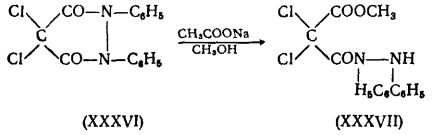
1,2,4,4-Tetrasubstituted pyrazolidine-3,5-diones with nitrogen-containing substituents no longer possess these properties because there are no hydrogen atoms attached to C_4 or N and these hydrogen atoms are required for enolisation or formation of an iminol. These compounds therefore form stable salts even with oxalic acid[118].

IV. STABILITY OF THE PYRAZOLIDINE-3,5-DIONE RING

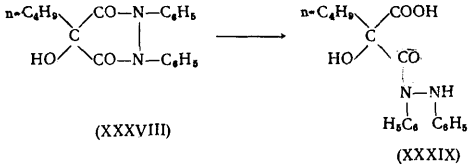
Stability towards acids and alkalis. Unsubstituted pyrazolidine-3,5-dione (III) is unstable and decomposes on boiling with strong mineral acids and alkalis, with liberation of hydrazine[7]. Substitution of the hydrogen atoms at C_4 and N stabilises the ring: mono-, di-, and tri-substituted pyrazolidine-3,5-diones are significantly more stable towards acids and alkalis[10,12,45,105], this being apparently connected with the greater stability of the enol and iminol forms. However, the C–N bond is broken on prolonged boiling of pyrazolidine-3,5-diones with anhydrous alcohols in the presence of anhydrous acids[119]. 1,2,4,4-Tetrasubstituted derivatives are less stable and decompose, with cleavage of the C–N bond, on boiling with alkalis[5,10,33]:



Tetrasubstituted pyrazolidine-3,5-diones with electronegative substituents, such as Cl or OH, at C_4 are particularly sensitive to alkaline reagents. 4,4-Dichloro-1,2-diphenylpyrazolidine-3,5-dione (XXXVI) is decomposed easily by sodium acetate at 20°:[120]

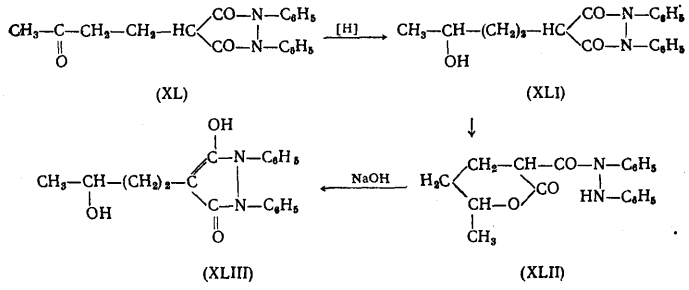


(XXXVI) (XXXVII)



(XXXVIII) (XXXIX)

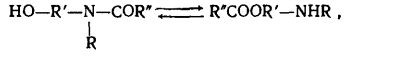
4-Hydroxybutadione (XXXVIII) is also unstable. It is decomposed by the action of dilute sodium hydroxide in the cold[121,122]. Boiling the decomposition product (XXXIX) with water leads again to ring-closure[123,124]. Recently, cleavage of the pyrazolidine-3,5-dione ring by reaction with hydrazines and amines has also been studied. Here again the C–N bond is broken[125]. Two products were isolated in the reduction of 4-(3-oxobutyl)-1,2-diphenylpyrazolidine-3,5-dione (XL); [107,126] their ultraviolet and infrared spectra and pK values showed that one of them is 4-(3-hydroxybutyl)-1,2-diphenylpyrazolidine-3,5-dione (XLI) and the other the *NN'*-diphenylhydrazide of the δ-lactone of α-carboxy-δ-hydroxyhexanoic acid (XLII):



(XL) (XLI)

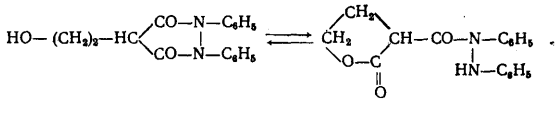
(XLIII) (XLII)

Similar conversions, which are instances of the general conversion of hydroxyalkylamides into aminoalkyl esters:



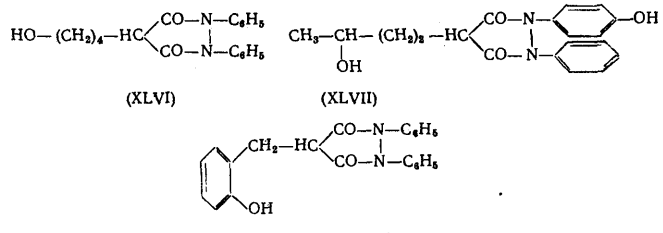
have been described previously[127].

The intermediate hydroxy-compound (XLI) is converted into the lactone (XLII) on treating it with dilute acids or on crystallisation, and (XLII) is converted into the tautomeric hydroxy-compound (XLIII) on treating the lactone with alkali. The 2-hydroxyethyl derivative (XLIV) behaves similarly, giving the γ-lactone (XLV):



(XLIV) (XLV)

Compounds with a hydroxy-group which is further away from C_4 along the side chain (XLVI), phenolic (XLVII), or an *o*-hydroxy-group in a benzyl radical (XLVIII), do not form lactones.



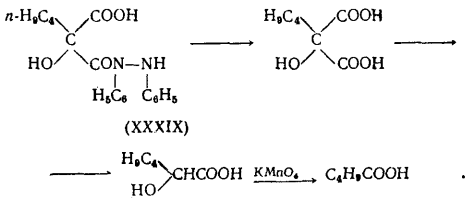
(XLVI) (XLVII)

(XLVIII)

Stability towards oxidising agents. Pyrazolidine-3,5-dione (III) is a strong reducing agent; for example, it reduces an ammoniacal solution of silver oxide even in the cold[7]. Substituents diminish the reducing power. Thus, Fehling's solution is reduced by 1-phenylpyrazolidine-3,5-dione (VI) only on heating[105] and by 1,2,4,4-tetrasubstituted derivatives only on boiling[38]. Cleavage of the ring with liberation of hydrazine evidently precedes reduction.

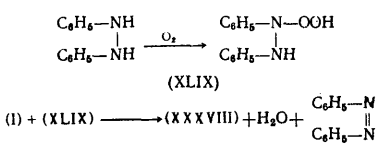
In milder oxidation the ring is not broken but is oxidised at C_4.[49,121-124,128-130].

The first careful and thorough investigation of the oxidation of 1,2-diphenylpyrazolidine-3,5-diones was carried out by Sokolova and Magidson[121,122] using Butadione (I). They showed that 4-hydroxybutadione (XXXVIII) is a by-product of the synthesis of (I). It was found that the oxygen carrier in the oxidation of Butadione is hydrazobenzene, in the presence of which Butadione is oxidised with yields up to 9%. 4-Hydroxybutadione breaks down to the mono(diphenylhydrazide) of butyltartronic acid (XXXIX), further degradation of which was also detected by the authors:



(XXXIX)

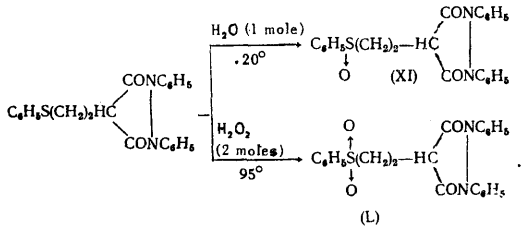
In repetitions of the experiments, Veibel *et al.*[128] could not isolate 4-hydroxybutadione but did isolate azobenzene and the hydrozide (XXXIX); they confirmed that hydrazobenzene is the oxygen carrier and that oxidation of Butadione takes place as follows:



(XLIX)

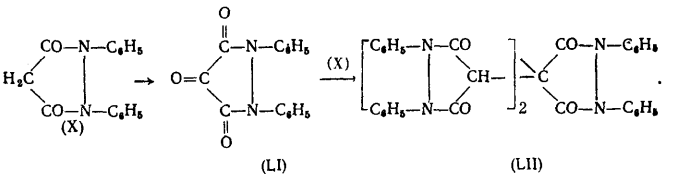
The oxidation scheme for Butadione[121,122] has been confirmed by other authors[123,124,129,130].

Extreme ease of oxidation at C_4 is characteristic also of other pyrazolidine-3,5-diones[124]; for example, 4-hydroxy--derivatives are obtained in up to 30% yield when oxygen is passed into gently boiling alcoholic solutions of these compounds. Under these conditions 1,4-diphenyl- and 1,2,4--triphenyl-pyrazolidine-3,5-dione were not oxidised. Veibel *et al.*[128] succeeded in obtaining 4-hydroxy-derivatives of 4-alkyl-1-phenyl- and 1,4-diphenyl-pyrazolidine--3,5-diones in 50–75% yields using oxidation in methanol solution in the presence of triethylamine. They found that the oxidation of pyrazolidine-3,5-diones is considerably more rapid than that of the corresponding pyrazol-5-ones. As the length of the alkyl chain attached to C_4 increases, the rate of oxidation falls, and a compound such as 1,2-diphenyl-4-tritylpyrazolidine-3,5-dione does not in general undergo oxidation; this is apparently connected with steric hindrance. It has been shown[36] that a sulphur atom in the side chain can be oxidised without oxidising C_4.



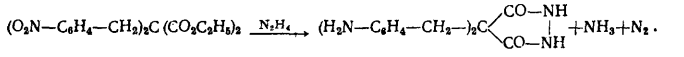
(L)

The oxidation of 1,2-diphenylpyrazolidine-3,5-dione (X) by selenium oxide in boiling dioxan has been studied recently[131]; a product of the condensation of the oxidised compound (LI) with the original substance was isolated:

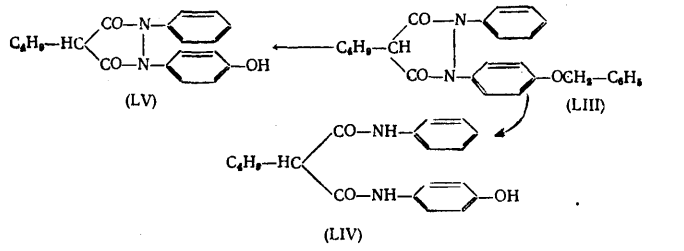


(LI) (LII)

Stability towards reducing agents. The pyrazolidine--3,5-dione ring is stable towards the usual reducing agents. It does not react with zinc dust/ammonium chloride[47] nor hydrogen/catalysts (Pd/C, Raney Ni, etc.) at ordinary or elevated temperatures (up to 80°) or at pressures up to 20 atm.[132-137] Moreover, the pyrazolidine-3,5-dione ring is formed under conditions where a nitro-group is reduced to an amino-group[138]:



However, whereas at low temperatures the benzyl group is removed from compound (LIII) without ring cleavage, at elevated temperatures the N–N bond is also broken to give the diamide (LIV):[45]



(LV) (LIII) (LIV)

Denss[139] observed a similar reaction in the reductive alkylation of pyrazolidine-3,5-diones.

V. ELECTROPHILIC AND NUCLEOPHILIC SUBSTITUTION REACTIONS

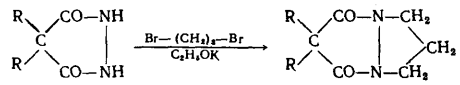
For partially substituted pyrazolidine-3,5-diones, electrophilic substitution of the hydrogen atoms at C_4, and to a lesser extent of those at the nitrogen atoms, is the most characteristic reaction. Depending on the nature of the electrophilic reagent and on the number and type of the substituents already present, substitution takes place at the C or N atoms; a completely substituted compound may be formed.

Alkylation, which is one of the most studied and frequently applied reactions, is used to obtain derivatives alkylated at C_4 and at the N atoms. When the mono- and di-substituted compounds are alkylated, depending on the conditions, both partially and completely substituted derivatives can be formed[3,5,10,17,33,134,140-142]. As Büchi and coworkers found[16], alkylation occurs first at C_4 and later at the N atoms, indicating that the hydrogen atoms at C_4 are more active than those at the N atoms. Various alkylating agents have been used: dialkyl sulphates[10], alkyl halides[3,5,16,33,143-146], substituted alkyl halides[147,148], α-halogenocarboxylic acids[149], tertiary alcohols[188], ethers[150], and diazomethane[109,151,152].

Alkylation is carried out at room temperature or slightly above[3,5,16] but sometimes by boiling with excess alkyl

halide[153]. The use of catalysts (BF_3, $AlCl_3$, $ZnCl_2$, $FeCl_3$) facilitates alkylation considerably[150,154].

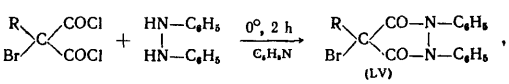
When *NN'*-unsubstituted pyrazolidine-3,5-diones are alkylated at the N atoms with 1,3-dibromopropane (or 1,4--dibromobutane) a bicyclic system which includes the pyrazolidine-3,5-dione ring is obtained[155]:

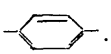


Halogenation and substitution with thiocyanate are the electrophilic substitution reactions at C_4 which occur most easily. From 4-unsubstituted pyrazolidine-3,5-diones both 4-mono- and 4,4-di-halogeno(or -thiocyanato)-derivatives can be easily obtained using the corresponding quantities of halogen or thiocyanogen[3,6,108,156].

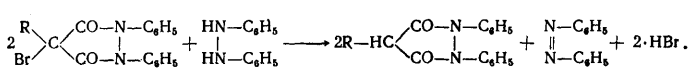
The presence of one alkyl or phenyl group at C_4 does not reduce the activity of the remaining hydrogen atom; these compounds also easily form 4-chloro- and 4-bromo-derivatives, both in the cold and on gentle heating in chlorinated hydrocarbons[3,120,157,158]. The preparations of 4-iodobutadione using iodine monochloride or iodine[159,160] and of 4-iodomethylbutadione by boiling with methylene iodide in an alkaline solution[118] have also been described.

Compounds of this same type (LV) are obtained in satisfactory yields by direct condensation of 4-alkyl-4-bromomalonyl dichloride with hydrazobenzene[44]:

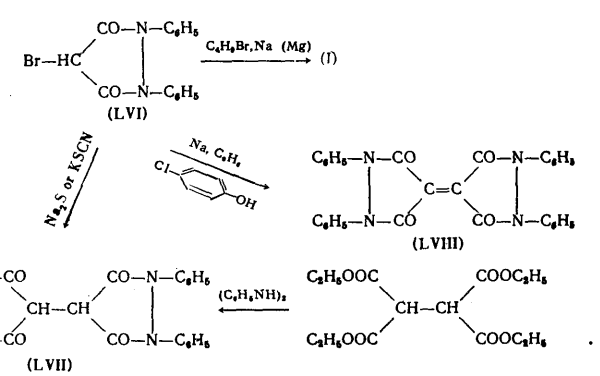


where R = C_2H_5, iso-C_3H_7, n-C_4H_9, C_6H_5, Cl-.

Compounds of type (LV) are easily dehalogenated on heating with hydrazobenzene. Because of this Mukherjee[42] was not at first able to obtain compound (LV) using an excess of hydrazobenzene:

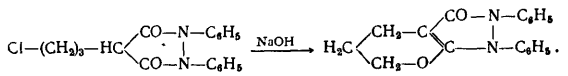


The great activity of the bromine is used to obtain various derivatives of compound (X):[44,161]



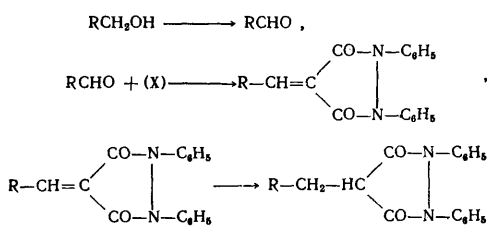
When compound (LVI) reacts with potassium thiocyanate, sodium sulphide, or triethylammonium diethylthiophosphate it does not form a substitution product but gives 1,2,1',2'--tetraphenyl-4,4'-bipyrazolidinyl-3,5,3',5'-tetraone (LVII), the structure of which has been demonstrated by synthesis[3,162]. Bromine is also removed from (LVI) by treating it with pyridine[3,162]. When (LVI) is boiled in benzene in the presence of sodium metal and *p*-chlorophenol a product which decolorises bromine and potassium permanganate solutions is obtained; structure (LVIII) is proposed for it[163].

In an alkaline medium, compounds containing a γ-halogenoalkyl chain at C_4 lose the halogen atom to form bicyclic compounds[164]:

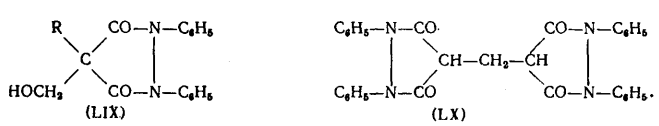


With aldehydes and ketones, 4-unsubstituted pyrazolidine-3,5-diones easily form 4-benzylidene, 4-isopropylidene , and other such derivatives[8,7,39,105,140,165], which are red substances which crystallise well. They are obtained by boiling pyrazolidine-3,5-diones with excess of the aldehyde or ketone; sometimes $ZnCl_2$ is used as catalyst[140]. Recently these unsaturated derivatives have often been used as intermediates, 4-monosubstituted pyrazolidine-3,5--diones being obtained by their reduction (generally catalytic)[140,143,166-168]. The latter compounds can also be obtained by alkylation with alcohols in the presence of catalysts, the water formed in the reaction being distilled off[169,170].

The reaction occurs in three stages[171]:

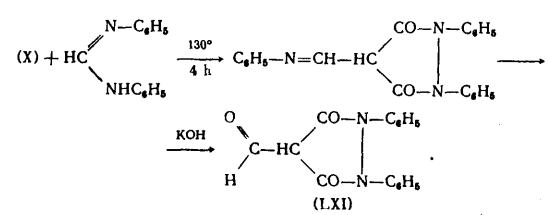


The separation of the condensation products with alkalis[39,165] and the relation between their colour and structure[172] have been studied. With formaldehyde, 4-monosubstituted 1,2-diphenylpyrazolidine-3,5-diones form 4-hydroxymethyl derivatives (LIX).[118,173,174]

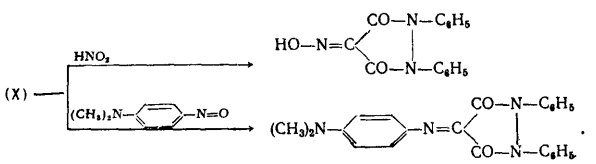


The reaction of one mole of formaldehyde with two moles of compound (X) gives unexpectedly bis-(1,2-diphenyl-3,5--dioxopyrazolidin-4-yl)methane (LX) and another substance, similar in composition but with a different melting point[3,162], which is evidently a polymer.

A pyrazolidine-3,5-dione containing an aldehyde group at C_4 (LXI) has also been described; it is obtained as follows[175]:

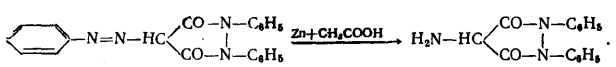


Nitroso- and isonitroso-derivatives of pyrazolidine-3,5-diones are easily formed in the reaction with nitroso(dimethylaniline)[162,176] or with sodium nitrite in acidic solution[7,13,105]. For example:



These compounds can be reduced to 4-amino-derivatives with ammonium sulphide[10,13] or zinc dust in acetic acid[108].

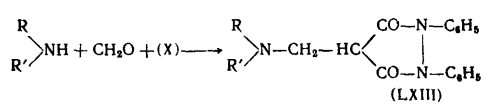
With diazonium salts, 4-unsubstituted and 4-monosubstituted derivatives give coloured azo-compounds in good yields; the products are stable to acids and alkalis under mild conditions[3,7,33,82,105,189], and they can be used for the synthesis of 4-aminopyrazolidine-3,5-diones (LXII):[109]



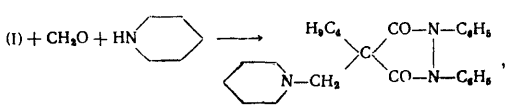
(LXII)

Compound (LXII) gives isopropylidene and acetyl derivatives[109].

In the *Mannich reaction* both 4-unsubstituted and 4-monosubstituted compounds can be used[110,118,177], giving respectively compounds of types (LXIII) and (LXIV):



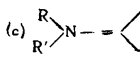
(LXIII)



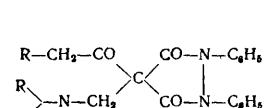
(LXIV)

where

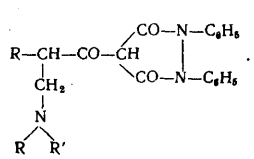
(a) $R = R' = CH_3$; (b) $R = CH_3$, $R' = H$;

(c)  (d) $R = C_4H_9$, $R' = H$.

The use of a 4-acyl derivative in the Mannich reaction does not give a 4,4-disubstituted compound (LXV) but one of type (LXVI):[177]

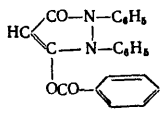


(LXV)

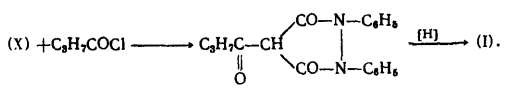


(LXVI)

Acylation of pyrazolidine-3,5-diones is one of the reactions most studied. In contrast to other electrophilic substitution reactions, acylation of 4-unsubstituted compounds gives only 4-monoacyl derivatives and no 4,4-disubstituted compounds are formed. It was originally thought[103] that these monoacyl compounds were *O*-acyl derivatives — *e.g.* (LXVII) — but it was soon shown[110,152] that when they are reduced, C_4-alkyl derivatives are formed, confirming that they have structures of type (LXVIII):



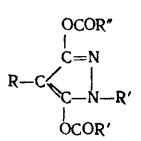
(LXVII)



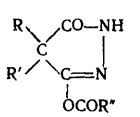
(LXVIII)

The infrared spectra of acylated compounds agree with these results[152].

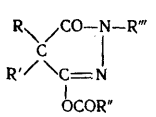
Acylation at the nitrogen atom in *N*-unsubstituted pyrazolidine-3,5-diones does not occur. When 1,4-disubstituted compounds are acylated, an *OO'*-diacyl derivative (LXIX) is obtained, and acylation of 4,4-di- and 1,4,4-tri-substituted derivatives gives compounds of types (LXX) and (LXXI):[10,12,33,49]



(LXIX)

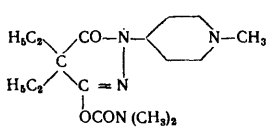


(LXX)

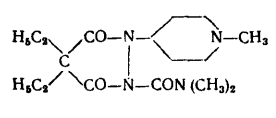


(LXXI)

These compounds were confirmed as *O*-acyl compounds from their infrared spectra and also by synthesis of alternative structures. For example, the acylation product (LXXII) differs in its properties from (LXXIII), which is obtained from an *NN'*-disubstituted hydrazine[49]:



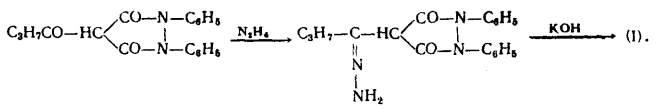
(LXXII)



(LXXIII)

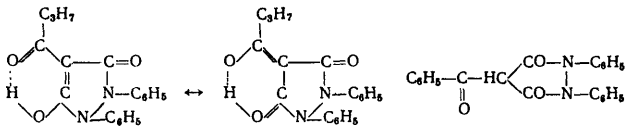
Acylation of 4-substituted 1,2-diphenyl-3,5-dioxopyrazolidines, for example (I), gives *O*-acylated derivatives, the structure of which is proved from the infrared spectra and by the ease of alkaline hydrolysis on boiling with an aqueous-alcoholic solution of potassium hydroxide[152]. Many 4-acylpyrazolidine-3,5-diones are described in a vast literature, particularly in patents[174,178-185]. Acylation is usually carried out by boiling the pyrazolidine-3,5-diones with excess acyl chloride or acid anhydride[12], sometimes in the presence of sodium acetate[10], and by the Schotten-Baumann[33] or Friedel-Crafts[177] reactions.

4-Acyl derivatives are used as intermediates for the synthesis of 4-alkyl-1,2-diphenylpyrazolidine-3,5-diones using the Kischner reaction[135,186,187]:



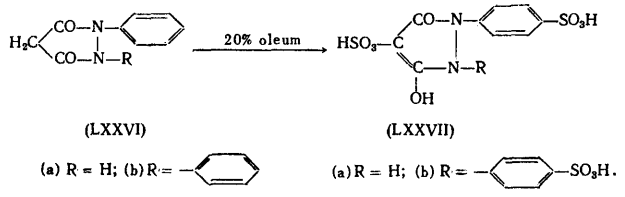
Reduction with lithium tetrahydroaluminate has also been described[177]. It was found from the infrared spectra

of 4-acyl-1,2-diphenylpyrazolidine-3,5-diones[110] that hydrogen bonding is marked in many of them (LXXIV), but the 4-benzoyl derivative is found in the trioxo-form (LXXV):[111]



(LXXIV) (LXXV)

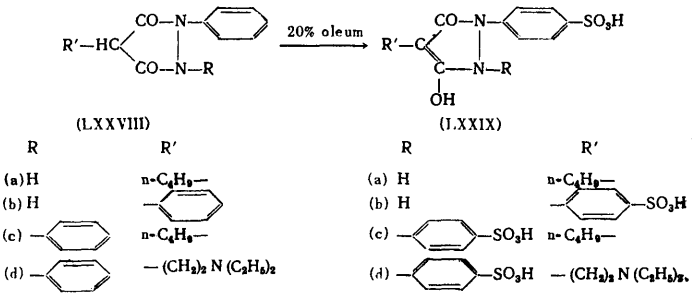
Sulphonation of pyrazolidine-3,5-diones has not been described, apart from exploratory results[3,189]. An investigation of the sulphonation of various types of pyrazolidine-3,5-dione by 20% oleum was begun only recently[190]. As with acylation, in the sulphonation of 4-unsubstituted compounds only one hydrogen atom at C_4 is replaced by the sulpho-group:



(LXXVI) (LXXVII)

(a) R = H; (b) R = (a) R = H; (b) R = .

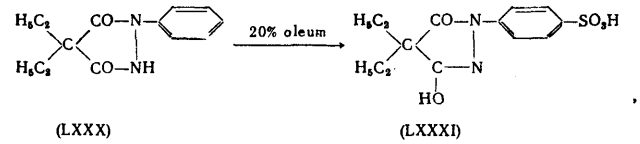
The sulpho-group at C_4 differs from the sulpho-group in aromatic sulphonic acids in that it is removed — from, for example, (LXXVIIa) and (LXXVIIb) — by the action of nitrous acid in the presence of $BaCl_2$, with formation of $BaSO_4$ quantitatively. 4-Monosubstituted pyrazolidine-3,5-diones (LXXVIIIa)-(LXXVIIId) are not sulphonated at C_4; only the hydrogen atom in the phenyl group is replaced. As shown by paper chromatography of the hydrolysates of the sulphonic acids, the sulpho-group enters only the *para*-position:



(LXXVIII) (I.XXIX)

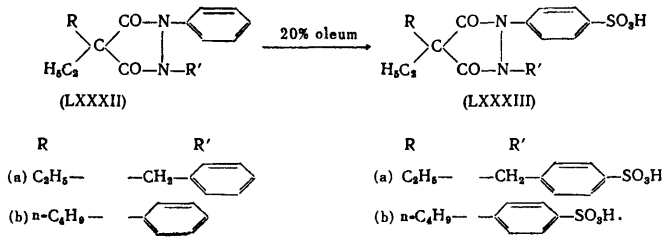
R	R′	R	R′
(a) H	n-C_6H_9—	(a) H	n-C_6H_9—
(b) H		(b) H	
(c)	n-C_6H_9—	(c)	n-C_6H_9—
(d)	—$(CH_2)_2N(C_2H_5)_2$	(d)	—$(CH_2)_2N(C_2H_5)_2$.

1,4,4-Trisubstituted compounds (LXXX) behave similarly:



(LXXX) (LXXXI)

and also 1,2,4,4-tetrasubstituted compounds (LXXXIIa) and (LXXXIIb):



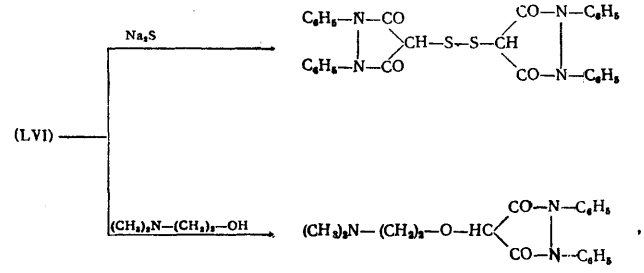
(LXXXII) (LXXXIII)

R	R′	R	R′
(a) C_2H_5—	—CH_2—	(a) C_2H_5—	—CH_2—
(b) n-C_4H_9—		(b) n-C_4H_9—	

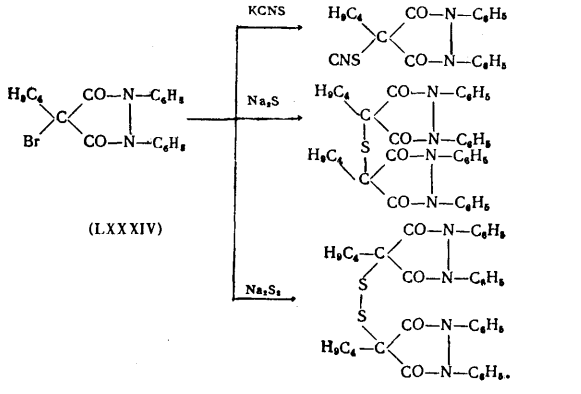
Introduction of a sulpho-group into the ring or into the phenyl group increases considerably the acidity of the enol, and also of the iminol, hydroxy-groups; they are salt-forming in all the sulphonic acids. This is especially so for a sulpho-group in a phenyl group at C_4 (LXXIXb). Whereas an alcoholic solution of the original compound (LXXVIIIb) gives only a slight green coloration with $FeCl_3$ solution, an aqueous solution of the sulphonic acid (LXXIXb) gives an intense blue colour.

Nitration of pyrazolidine-3,5-diones has hardly been studied. Nitration of compound (X) with excess of a nitrating mixture at 0° gives a tetranitro-derivative[108], but with a smaller quantity of the nitrating mixture it gives a mononitro-derivative[3,189]. Although it can be assumed in the latter case that the nitro-group is attached to C_4, this hypothesis requires proof.

Nucleophilic substitution reactions of derivatives of pyrazolidine-3,5-diones have also been little studied. Substitution of the bromine in 4-bromo-1,2-diphenylpyrazolidine-3,5-dione (LVI) has been described[108,163],



and also substitution in 4-bromo-4-n-butyl-1,2-diphenylpyrazolidine-3,5-dione (LXXXIV).[3,156,163].

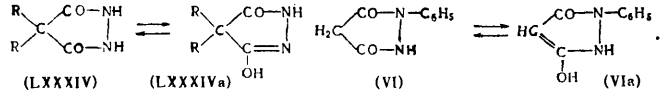


(LXXXIV)

VI. THE CHARACTER OF THE PYRAZOLIDINE-3,5--DIONE RING

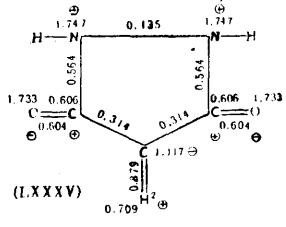
Various opinions have been expressed concerning this question. One considers that the pyrazolidine-3,5-dione ring is similar to aromatic amines[3,189]; most authors do not consider the interaction of the hydrazine part of the molecule with the β-dicarbonyl part.

Arndt[191] made a special study of the character of the pyrazolidine-3,5-dione ring. He concluded, from a comparison of the chemical properties of various hetero-rings containing two nitrogen atoms, that compounds like 4,4-diethylpyrazolidine-3,5-dione (LXXXIV) are not capable of aromaticity but compounds like 1-phenylpyrazolidine-3,5--dione (VI) are, because the enol form (VIa) possesses a sextet of π electrons:



(LXXXIV) (LXXXIVa) (VI) (VIa)

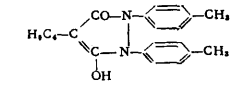
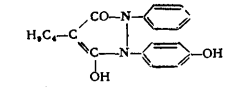
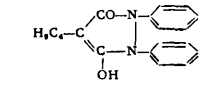
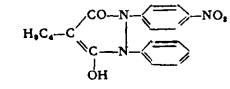
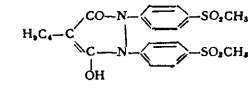
As seen from the above review of chemical properties and methods of preparation, pyrazolidine-3,5-diones in fact show a number of features characteristic of aromatic systems, namely: the system is fairly stable (particularly towards reduction), the hydrogen atom at C_4 is easily substituted in innumerable electrophilic substitution reactions, and finally 4-unsubstituted and 4-monosubstituted compounds display similarities to phenols on sulphonation. However, not one of these properties can serve as a strict criterion of aromaticity[192] because non-aromatic compounds may also possess them, as has been shown particularly clearly in a recent series of papers on cyclic β-diketones[193]. Nevertheless there are results which agree with the hypothesis of the aromatic character of the pyrazolidine-3,5--dione ring. For example, Besnainou and Chalvet[194] give a molecular diagram for pyrazolidine-3,5-dione (LXXXV) obtained by the molecular-orbital method, in which the π bond indices show that, to a considerable extent, the bonds in the ring are averaged out, there being neither "pure" double nor single bonds; this is characteristic of non-benzenoid aromatic systems[192].



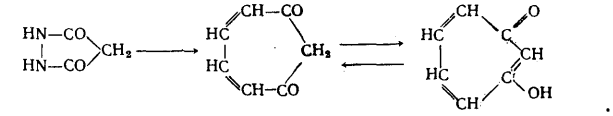
(LXXXV)

There are also other data which support the aromatic character of pyrazolidine-3,5-diones, in particular those concerning the effect of substituents in the *para*-position of the phenyl groups in 4-n-butyl-1,2-diphenylpyrazolidine--3,5-dione (I) on the pK_a values of these compounds (see Table)[195,196]. Electron-donor substituents (CH_3, OH) reduce and electron-acceptor substituents (NO_2, SO_2CH_3) increase the degree of dissociation of the enol hydroxy-group. This behaviour can be explained precisely by aromatic character of the hetero-ring, which can allow the effect of substituents in the remote *para*-position of the phenyl group to be transmitted to the enol hydroxy-group of the hetero-ring through the nitrogen and carbon atoms.

TABLE. Relation between pK_a for Butadione derivatives and the substituents in the *para*-position of the phenyl groups.

Formula	pK_a
	4.9
	4.7
	4.5
	3.2
	2.7

If the two nitrogen atoms in the pyrazolidine-3,5-dione ring are replaced by two equivalent –CH=CH– groups, we obtain system LXXXVI, the enol form of which (LXXXVII) strongly recalls tropolone:



(LXXXVI) (LXXXVII)

In this connection it is of interest that azulene, which contains a seven-membered ring and is, in our opinion, related to pyrazolidine-3,5-dione possesses, like the latter, antiphlogistic activity[197].

Thus on the basis of available data, it can be assumed that pyrazolidine-3,5-diones also belong to the class of non--benzenoid aromatic systems which possess in addition properties typical of compounds with an active methylene group.

VII. APPLICATIONS OF PYRAZOLIDINE-3,5-DIONES

Pyrazolidine-3,5-diones have had a very wide application in medicine. Besides Butadione (I), which is used extensively to treat rheumatic and inflammatory illnesses[198-200], 1,4-diphenylpyrazolidine-3,5-dione (LXXVIIIb), 4-n-butyl--2-*p*-hydroxyphenyl-1-phenylpyrazolidine-3,5-dione (LV), and 1,2-diphenyl-4-(β-phenylsulphinylethyl)pyrazolidine--3,5-dione (XI) are used clinically. Besides the large number of papers devoted to a thorough study of the biological properties of Butadione, there are a number on the pharmacological properties of other representatives of this

group[201-207]. However, the total number of pharmacological tests which have been made is comparatively small. In addition, different workers have used different methods to test for antiphlogistic activity, the most valuable property of pyrazolidine-3,5-diones. Consequently, the results produced for the same compound by different workers do not always agree. The relation between structure and physiological activity in these compounds is not known definitely although the available data permit certain conclusions to be made:

(1) The pyrazolidine-3,5-dione ring possesses specific antiphlogistic action because replacement of the nitrogen atoms in the ring by carbon produces inactive compounds[201].

(2) Substitution of the oxygen atom of a carbonyl group by sulphur does not impair the antiphlogistic and antipyretic properties of pyrazolidine-3,5-diones[204].

(3) Introduction of substituents, *e.g.* a carboxylic acid group, into the phenyl group of compounds of the Butadione type reduces their toxicity markedly[201]. A sulphonic acid group in this position reduces the toxicity even more[190,208]. Such compounds — (LXXIXa)–(LXXIXc), (LXXXI) — are practically non-toxic to animals.

(4) The most active compounds in a series of 1-phenyl- and 1,2-diphenyl-4-monoalkylpyrazolidine-3,5-diones are the 4-n-butyl derivatives.

In addition a number of compounds with other substituents at C_4 which are not worse than, and sometimes even surpass, Butadione in antiphlogistic activity and which are also less toxic have been synthesised. They are, for example, 1,2-diphenylpyrazolidine-3,5-diones containing 4-(γ-hydroxybutyl)[209], 4-(γ-oxobutyl)[210], and 4-diethylaminoethyl[206] groups.

The relation between pK_a and uricolitic activity found in a series of 4-monosubstituted 1,2-diphenylpyrazolidine-3,5-diones[195,196] is of great interest and may prove useful in the search for new uricolitics.

Methods of qualitative and quantitative analysis have been developed for pyrazolidine-3,5-diones. The available data on their characteristic colour reactions concern mainly compounds used in medicine[211-215]. Paper chromatography is often used for analysis. Originally water-saturated systems containing butanol or benzene[216,217] were used for the development but the use of water, in which the solubility of Butadione is only 1 : 11 000,[211] as the stationary phase did not give satisfactory results since the R_f values were then close to 1. Chromatographic methods were soon developed in which the paper was impregnated with a non-aqueous phase, *e.g.* a 50% solution of formamide in acetone or a 2.5% solution of petroleum jelly in ether[218], or a tartrate buffer[219]. This method was found to be useful in an industrial laboratory[220,221].

Quantitative determinations include gravimetric[220,222] volumetric[159,211,212,223,224], and spectrophotometric[188,218,225,226] methods and the microdetermination of nitrogen[211].

It was discovered recently that, apart from the range of effects valuable in the treatment of rheumatic and inflammatory illnesses, pyrazolidine-3,5-diones also possess other interesting properties, in particular selective insecticidal action[227-230]; the 4,4-dichloro-derivatives possess hypoglycemic action[120]. Pyrazolidine-3,5-diones are used as solubilising media[59,231,232] for water-insoluble medicinal preparations, and also in colour photography[233-236] and as antioxidants[237].

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U.D.C. 547.97 : 541.6

INTERACTION OF DYES WITH SUBSTANCES OF HIGH MOLECULAR WEIGHT

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1. INTRODUCTION

In the technically important problem of the interaction of macromolecular substances (polymers) with complicated organic dye molecules, which underlies the dyeing of animal and vegetable fibres, we encounter combinations of various types of polymers and of dyes, both ionogenic and non-ionogenic; each individual case must be expected to have its own mechanism of interaction and its own type of bonding.

Increasing attention has recently been paid to a particular aspect of this problem — the interaction of polymer and dye *ions*, with an electrostatic type of bonding. We come up against this in practical work in various branches of chemistry, for example photographic chemistry in the optical sensitisation of photographic emulsions, histochemistry in the use of staining to differentiate tissues, and finally in the chemistry of surface-active agents in identification of the latter with dyes.

In all cases we are concerned with the same phenomenon — a change in the absorption spectrum (and also in the intensity of fluorescence) of the dye, which produces a change in colour of the material (in histochemistry this phenomenon has been termed "metachromasy" — for reviews see Refs. 1–4). This makes the application of the spectroscopic method of investigation especially fruitful.

In each of the above fields the use of this technique has led to definite advances, but nevertheless difficulties arise in practical work, indicating that insufficient study has been made of the problem. In several cases the results in different fields supplement one another; a detailed comparison of them should contribute to further progress. The purpose of the present review, which examines all the results obtained from a unified viewpoint, is to report the present position of the problem of the interaction of ionogenic high polymers and dyes in the above fields.

The fundamental condition for the formation of new absorption bands in the interaction of polymer and dye ions is that the ions should bear charges of opposite sign. Few data are available on the interaction of anionic dyes with cationic polymers; the combination of cationic dyes with anionic polymers has been studied to the greatest extent, and it is there that the main generalisations have been made.

Before passing to an account of work on the changes undergone by the spectra of dyes on interaction with polymers, we should briefly recall the properties of the most typical polymers (termed "chromotropes" in the literature on metachromasy), and also the spectral properties of the dyes employed.

2. MACROMOLECULAR SUBSTANCES PRODUCING A CHANGE IN THE COLOUR OF A DYE ("METACHROMASY")

Numerous investigations show[3] that, in addition to actual macromolecular substances of high molecular weight, substances of low molecular weight which can associate to form micelles of high molecular weight, are also effective.

Chromotropes of the first type include macromolecular electrolytes[5,6] from various sources; substances of anionic character investigated include polyelectrolytes of animal[7] (heparin†, chondroitin sulphate, hyaluronate, nucleic acids) and vegetable (agar-agar[8], alginates) origin, inorganic (silicates, polyphosphates), and finally synthetic (chitin sulphate, carboxymethylcellulose, polyacrylates). These polymeric substances contain hundreds of ionogenic groups

† Heparin is a substance, formed in the liver, which diminishes the coagulability of blood.