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The Carbon-Nitrogen Triad Prototropic Tautomerism

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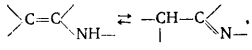
Data on the imine-enamine and related types of tautomerism are surveyed and different approaches to problems of the tautomerism of enamides, which play a major role in biological processes, are examined.
The bibliography includes 98 references.

CONTENTS

I.	Introduction	107
II.	The imine-enamine tautomerism	108
III.	The hydrazone-enehydrazine tautomerism	111
IV.	The tautomerism of certain enamines with *N*-functional group substituents	111
V.	Certain approaches to the problem of the enamide-*N*-acylimine tautomerism	112

I. INTRODUCTION

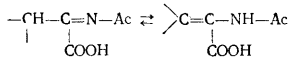
Systematic studies on the carbon–nitrogen triad prototropic tautomerism have been carried out for little more than ten years. As a result of the development of spectroscopic techniques, particularly NMR spectroscopy, quantitative data have been obtained during this period concerning the influence of internal and external factors on the position of the equilibrium



(1)

The major role of unstable tautomeric *N*-acylimino-forms as reactive intermediates has been demonstrated and many reactions have been examined from the standpoint of the involvement of both tautomeric forms. The tautomeric equilibrium constants and the energies of the tautomers have been obtained by kinetic and computational methods.

There has been a considerable growth of interest in the last five years in the study of the enamide–*N*-acylimine tautomerism in connection with research on α-carboxy-enamides (*N*-acyldehydroamino-acids), since it has been observed that such structures are present in natural peptides. A direct relation between the enamide–*N*-acylimine tautomerism



(2)

and the reactions occurring in living organisms (the synthesis and hydrolysis of peptides, the racemisation of natural amino-acids, the metabolism of antibiotics, etc.) has been demonstrated. Methods for the synthesis of penicillins substituted by functional groups at $C_{(6)}$ have been developed on the basis of the formation of reactive intermediate *N*-acylimines.

Bearing in mind the great importance of these studies and the lack of a complete review devoted to the enamine–imine tautomerism, we surveyed the literature published

up to October, 1976, in order to draw attention to this interesting and hitherto little studied field of organic chemistry. Of the earlier publications, we may mention Layer's review[1] of imines in which reactions confirming the possibility of the transformation of imines into enamines are surveyed; there have been no direct observations of the tautomeric equilibrium by physical methods at that time[1].

II. THE IMINE–ENAMINE TAUTOMERISM

Equilibrium (1) has been studied quantitatively mainly for imine–enamine systems and to a lesser extent for iminoesters and hydrazines; there have been only isolated studies on enamines with N-functional group substituents. We shall therefore consider below a quantitative assessment of equilibrium (1) for simple systems and then certain approaches to problems of the tautomerism of enamines with N-functional group substituents.

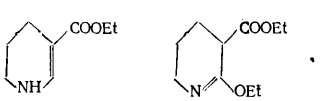
1. The Influence of Substituents in the α-Position

It has been noted in a number of studies that various alkyl substituents in the α-position have a weak influence on the equilibrium position. On passing to aliphatic-aromatic and then to aromatic substituents, the equilibrium usually shifts towards the enamine[2-4], which shows that an α-substituent capable of non-polar conjugation promotes the formation of the enamine (see also Bourbon et al.[5]). However, an approximately 1 : 1 ratio of the two forms for R = CH_3, $CH_2C_6H_5$, and C_6H_5 has been found[6] for the equilibrium

$$C_6H_5-CH=\underset{\displaystyle R}{\underset{|}{C}}-NH_2 \rightleftarrows C_6H_5-CH_2-\underset{\displaystyle R}{\underset{|}{C}}=NH \quad . \qquad (3)$$

The influence of α-substituents is manifested more clearly on passing to α-alkoxyenamines.[7,8]

The introduction of an OR group instead of the hydrocarbon residue into the enamine $C_6H_5CH=C(R)-NH_2$ wholly displaces the equilibrium towards the iminoform[7]; the compound exists as the iminoester $C_6H_5CH_2C(=NH)OR$. The same has been found[8] for the tetrahydronicotinate ester, which exists as the enamine, while its α-ethoxy-derivative exists in the imino-form:



The introduction of a thio-group in the α-position also leads to a high content of the imino-form (up to 70%) [9] (the imino-form is usually absent in the presence of strong electron acceptors in the β-position[4]). When the α-substituents were varied in the system

$$C_6H_5NH-\underset{\displaystyle SR}{\underset{|}{C}}=C(COOEt)_2 \overset{K}{\rightleftarrows} C_6H_5-N=\underset{\displaystyle SR}{\underset{|}{C}}-CH(COOEt)_2 \quad , \qquad (4)$$

a correlation was observed[9] between $\lg K$, on the one hand, and the σ^* constants and the basicity of the enamines on the other: $\lg K = 0.614 - 0.24\sigma^*_R$; $\lg K = -2.992 + 0.34pK_a$. The first expression indicates a very weak dependence of K on the nature of the residue R, which leads to the conclusion that the nature of the atom linked directly to the carbon atom in the α-position has a decisive influence on equilibrium (1).

2. The Influence of Substituents in the β-Position

Substituents attached to the tautomeric centres (i.e. to the β-carbon atom and the nitrogen atom) have a greater influence than substituents at the central atom of the tautomeric system (the α-carbon atom). This is clearly seen from a comparison of the data of Bourbon et al.[5] and Ahlbrecht and Fischer[10]. Thus the content of the enamine form varies from 50 to 67% for α-substituted compounds $CH_3-CH=CRNH_2$ (R = 2-, 3-, or 4-pyridyl), while the variation for the β-substituted analogues is within the wider range from 33 to 100%.[10]

The influence of substituents in the β-position such as NO_2, CN, CO, etc.[4] is such that the imine form is absent. The replacement of the methylgroup in the β-position by the phenyl group also causes a sharp shift of the equilibrium towards the enamine[4,6].

The dependence of equilibrium (1) on the nature of the substituents in the β-position has been studied in detail for a series of enamines $RC_6H_4C(CH_3)=CHNHAr$.[11,12] It was shown that electron-donating substituents shift the equilibrium towards the imine, the shift depending on the solvent: it is greater in polar nitrobenzene than in non-polar bromobenzene.

The introduction of a strong electron-accepting group (R^1 = CN) in the β-position of the iminoesters $R^1CH_2C.(=NR)OR^2$ leads to the appearance of the enamine form, while for R^1 = Ar the compound consists of the pure imine[7].

The increase of the bulk of the R^1_2N group in the enediamines $R^1_2NCH=C(C_6H_5)NHR$ leads to a sharp increase of the content of the enamine and, when R^1_2N = 2,6-dimethylpiperidino, the imine is not detected at all, whereas for $R^1_2N = N(CH_3)_2$ the fraction of the imine is 91%.[13]

3. The Influence of Substituents at the Nitrogen Atom

Analysis of the influence of substituents at the nitrogen atom on equilibrium (1) is of greatest interest, because it makes it possible to build a logical "bridge" from the imine–enamine systems which have been fairly thoroughly investigated to the enamide–N-acylimine system which have been little studied but are extremely important.

The study of the equilibrium (5)

$$R-CH=CR^1-NHC_6H_4-X \rightleftarrows R-CH_2CR^1=N-C_6H_4-X \qquad (5)$$

showed[4] that electron-donating substituents X in the benzene ring shift the equilibrium towards the imine form. The sensitivity to this influence increases in polar solvents (DMSO > pyridine > CCl_4).

An analogous relation for N-aryl-substituted tautomeric systems has been found also in a number of other studies[12,14-16]. N-Alkyl substituents shift equilibrium (1) towards the imine form compared with aromatic substituents[11,14,15]. This permits a conclusion important for subsequent exposition: the conjugation of the lone electron pair of the nitrogen atom with the substituent displaces equilibrium (1) towards the enamine tautomeric form.

A qualitatively analogous picture has been obtained for equilibrium (6) [2]:

$$(CH_3)_2CH-\underset{\displaystyle R}{\underset{|}{C}}=NR^1 \rightleftarrows (CH_3)_2C=\underset{\displaystyle R}{\underset{|}{C}}-NHR^1 \quad . \qquad (6)$$

The authors[2] analysed the relation between the equilibrium position and the π charge on the nitrogen atom in the imine form. A satisfactory correlation has been

observed between the imine content and the π charge on nitrogen: the greater the π charge, the smaller the imine content in the equilibrium mixture.

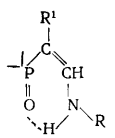
An attempt has been made[3] to find a relation between the content of the enamine and its pK_a. A parallel variation of these quantities has been observed qualitatively although no correlation could be found. Nevertheless, one may conclude that the greater the mobility of the proton in the amino-group the greater the shift of the equilibrium towards the enamine. Since any tautomeric prototropic equilibrium is always displaced towards the less acid form, one may reach an important and unexpected conclusion on the basis of the results of Savignac et al.[3]: the CH acidity of the imine increases to a greater extent than the NH acidity of the enamine as the electron-accepting properties of the substituents at the nitrogen atom are enhanced.

Apart from the electronic effects one should also note the influence of steric factors on the position of equilibrium (1). An increase of the bulk of the substituent R in the enediamines $R^1_2N-CH=C(C_6H_5)-NHR$ leads to an increase of the content of the enamine[13].

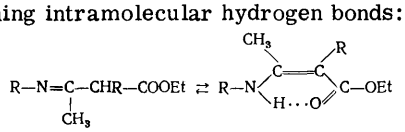
In contrast to the above data, the introduction of aromatic substituents at a nitrogen atom instead of aliphatic substituents in β-phosphorylated enamines

$>P(=O)CR^1=CHNHR$ shifts the equilibrium towards the

imine form; in the R = Ar series electron-accepting substituents in the ring displaces the equilibrium in the same direction[17-19]. Unfortunately the authors do not explain this contradiction between their data and literature results, although they do note a feature of the structure of enamines—the presence of an intramolecular hydrogen bond (IAHB):



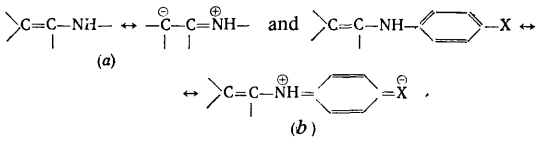
Yakimovich and coworkers[20,21] investigated other systems containing intramolecular hydrogen bonds:



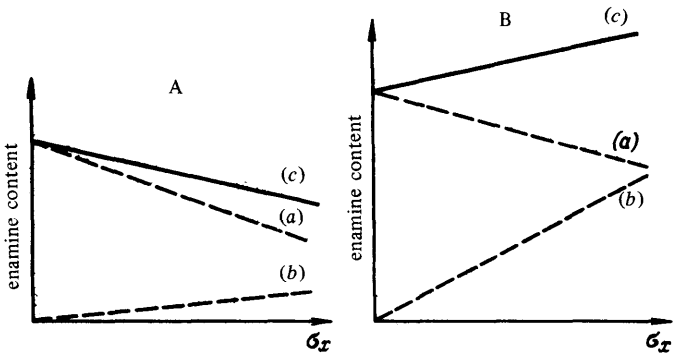
(7)

and also found a situation which is the opposite of that for enamines without such bonds. The authors explained this finding by the fact that the equilibrium position for simple imine–enamine systems[2,4,11-14] is determined by the stability of the enamine form, while in the presence of an IAHB[17-21] it is determined by the stability of the imine form, because the benzene ring in the enamine is not conjugated with nitrogen for steric reasons. The conjugation of the lone electron pair of the nitrogen with the benzene ring is easier than the conjugation of the C=N bond, so that in the absence of an IAHB the electron-accepting substituents stabilise the enamine form to a greater extent than the imine form and displace the equilibrium towards it. In the presence of an IAHB the conjugation in the enamine vanishes and electron acceptors stabilise only the imine, shifting the equilibrium in its direction.

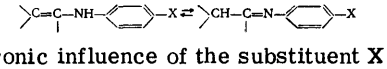
We believe that the simplest and convincing explanation of the unusual behaviour of systems containing electron-accepting groups (C=O, P=O, etc.) in the β-position has been given by Walter and Meyer[22], who considered two mechanisms of the stabilisation of the enamine:



Electron-accepting substituents in the benzene ring promote stabilisation via mechanism (*b*) and act against stabilisation via mechanism (*a*). In the presence of strong electron-accepting groups in the β-position, where the mechanism (*a*) should play an important role, electron-accepting substituents at the nitrogen atom therefore decrease the stability of the enamine and displace the equilibrium towards the imine, which has in fact been observed for such systems[17-21]. This is illustrated graphically in the Figure. The straight line (*c*), which summarises the influence of the substituent at the nitrogen atom on both stabilisation mechanisms [(*a*) and (*b*)], has a negative slope for strong electron-accepting substituents in the β-position. As their electron-accepting properties are weakened, the contribution to stabilisation via mechanism (*b*) increases and the slope of line (*c*) diminishes. This is consistent with the results of other studies[2,4,11,12,14-16].

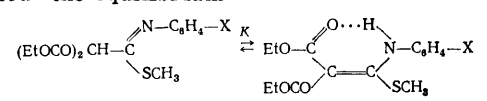


Dependence of the position of the equilibrium



on the electronic influence of the substituent X [22]: A) in the presence of strong electron-accepting substituents in the β-position; B) in the absence of such substituents.

To confirm their conclusions, Walter and Meyer investigated[9] the equilibrium



(8)

and found the following correlation with a negative slope ρ

ρ : $\lg K = 0.534 - 0.61\sigma_X$ ($r = 0.994$; $s_0 = 0.03$).

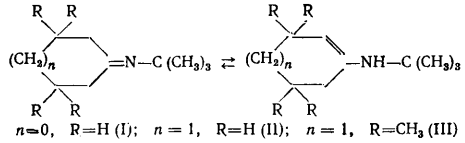
4. The Influence of the Solvent

Two tautomeric forms $C_6H_5-CH(CH_3)-N=C(CH_3)-CH_2COOEt$ and $C_6H_5-CH(CH_3)-NH-C(CH_3)=CHCOOEt$, which form an equilibrium mixture after standing for a

time, were isolated separately in one of the early studies[23]. Equilibrium is established faster in non-polar solvents than in polar solvents. Compared with methanol, pyridine displaces the equilibrium towards the enamine, while acetic acid displaces it towards the imine, which has been explained[23] by the greater basicity of the imine form.

A shift of equilibrium towards the enamine has been observed in many instances in polar solvents: in nitrobenzene relative to bromobenzene[11] and in DMSO relative to benzene [10] or carbon tetrachloride.[24] Ahlbrecht[25] showed that the content of the enamine $CH_3NHC(C_6H_4NO_2) = CHC_6H_4NO_2$ in the tautomeric mixture increases in the following sequence of solvents: $CHCl_3 < C_6H_6 < CH_3NO_2 < CH_3CN <$ acetone $<$ pyridine $<$ DMSO. Evidently a single monotonically varying characteristic cannot be isolated in the above series; this is understandable, because the equilibrium position is influenced both by the solvent polarity and by the ability of the solvent to form hydrogen bonds, as well as other types of specific solvation. Studies on iminoesters showed[7,26,27] that DMSO displaces the tautomeric equilibrium towards the enamine relative to nitrobenzene or dimethylformamide (DMF). The imine–enamine equilibrium constant for the imines $RCH_2CR^1{=}NR^2$ increases on passing from carbon tetrachloride to pyridine and then to DMSO.[4] In other cases the equilibrium also shifts towards the enamine in polar solvents (DMSO, nitrobenzene) relative to non-polar solvents ($CDCl_3$, CCl_4).[6] An attempt to investigate the influence of the solvent was also undertaken by Savignac et al.[3], but, since the imine form greatly predominates in the mixture (up to 95%) and the solvent has only an insignificant influence, the results are difficult to interpret unambiguously.

The series of solvents corresponding to an increasing content of the enediamine $C_4H_9NH-C(C_6H_5){=}CH-N(CH_3)_2$ in the equilibrium mixture is somewhat different[13]: $C_6D_6 < CDCl_3 <$ DMSO $<$ pyridine. The influnece of solvents on the equilibrium position has been studied for the cyclic five- and six-membered imines (I)–(III) [28]:



$n=0$, R=H (I); $n=1$, R=H (II); $n=1$, R=CH_3 (III) .

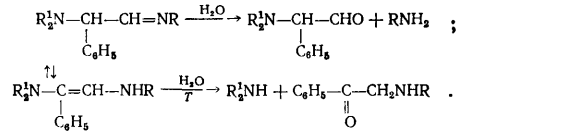
The following series of solvents which cause a shift of the equilibrium to the right has been found for (III): $CD_3OD < CDCl_3 < CH_2Cl_2 < CD_3NO_2 < CD_3CN < C_6H_5NO_2 < CCl_4 < C_6D_6 <$ pure substance $<$ acetone $<$ dioxan $<$ pyridine $<$ DMF $<$ DMSO $<$ cyclohexane. The series is fairly heterogeneous but it is nevertheless possible to distinguish two main tendencies in it: an increase of polarity and of the ability to accept a proton with formation of an intermolecular hydrogen bond (IRHB) from left to right (cyclohexane deviates from this relation). For compounds (I) and (II), the series of solvents investigated are shorter but the qualitative relation is the same.

Hence the ability of the solvent to form intermolecular hydrogen bonds as a rule stabilises the enamine form. The only exception is enamines with an electron-accepting group (C=O or P=O) in the β-position, which gives rise to an IAHB.[17–19]. In these cases solvents forming intermolecular hydrogen bonds disrupt the stable six-membered ring with an IAHB and destabilise the enamine. Thus the compounds $(iso\text{-}C_3H_7O)_2P(=O)CH{=}CH{-}NHR$ which exist as enamines in carbon tetrachloride, are converted into the corresponding imines in tributyl phosphate[17–19]. Similarly the following series of solvents, increasing the content of the imine form, has been found for equilibria (4) and (8): $CCl_4 \leqslant CDCl_3 \leqslant C_6D_6 < C_6D_5NO_2 < CD_3OD <$ DMSO $<$ pyridine $< CD_3NO_2 \simeq$ acetone.

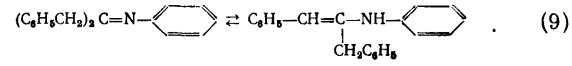
5. The Influence of Temperature

This problem has been studied less than others, although in the investigation of tautomeric equilibria it is very important, since information about the process energetics, the stabilities of individual forms, the entropies of transition of one form into another, etc. can be obtained from the temperature dependence.

The content of the enediamine $C_4H_9NH-C(C_6H_5){=}CH-N(CH_3)_2$ increases from 21% at -25° to 65% at 36°C.[13] This yields the difference between the energies of the tautomeric forms (not calculated by the authors) as $\Delta E = 5$ kcal mole^{-1}, the imine form having a lower energy in this instance. The results of physicochemical analysis have also been confirmed by chemical transformations[13]: hydrolysis to the aldehyde and the amine proceeds in the cold, while on heating the substance is converted into the aminoketone via the following mechanism:



Töke and coworkers[26,27] studied the influence of temperature on the position of the tautomeric equilibrium for iminoesters in DMF and DMSO. $\Delta E = 2.8$ kcal mole^{-1} in DMF and $\Delta E = 4.2$ kcal mole^{-1} in DMSO may be calculated from the data which they obtained. In this case the enamine form is energetically more favourable. An increase of the imine content with increasing temperature was also noted by Ahlbrecht[25]. The following equilibrium in DMSO has been studied over a wide temperature range[24]:



(9)

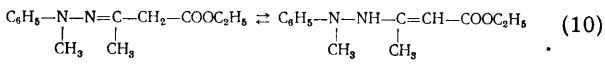
The energy difference (not calculated by the authors) is small (2.3 kcal mole^{-1}), the enamine having a smaller energy than in other studies[25–27]. The temperature dependence of equilibrium (4) has been studied for $R = CH_2C_6H_5$ in $CDBr_3$ and $C_6D_5NO_2$.[29] The parameters $\Delta H^\circ = 3.59$ kcal mole^{-1} and $\Delta S^\circ = 9.35$ cal mole^{-1} K^{-1} in $CDBr_3$ and $\Delta H^\circ = 2.60$ kcal mole^{-1} and $\Delta S^\circ = 6.87$ cal mole^{-1} K^{-1} in $C_6D_5NO_2$ were found; the relative stabilities of the tautomeric forms are analogous to those observed in other studies[24–27].

The influence of paramagnetic additives on the position of the tautomeric equilibrium studied in relation to cyclohexanone imines should also be mentioned[30]. The addition of the europium complex $Eu(fod)_3$ shifts the equilibrium towards the imine, which indicates a greater basicity of the imine form (cf. Potapov et al.[23]). Analysis of the literature data for the tautomerism of simple imine–enamine systems permits certain general conclusions. In the absence of conjugation with an electron-accepting substituent the imine form is more stable. Conjugation with an electron-accepting substituent in any position stabilises the enamine. Solvents forming intermolecular hydrogen bonds displace the equilibrium towards the enamine, apart from the instances where the enamines contain an IAHB; in such systems the solvent has the opposite influence. In the absence of conjugation with electron-accepting groups the imine–enamine equilibrium

constant increases with temperature, while in the presence of such conjugation it diminishes. Finally, the conversion of one tautomeric form into another involves an intermolecular proton transfer, because the intramolecular process is forbidden by the Woodward–Hoffmann orbital symmetry rules[8].

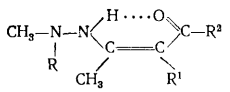
III. THE HYDRAZONE–ENEHYDRAZINE TAUTOMERISM

We shall consider briefly, in addition to the foregoing, the tautomerism of *N*-aminoimines (hydrazones), discovered by Ahlbrecht[31] in relation to the equilibrium



(10)

It has been shown for the compounds $(CH_3)_2NNH-CR^1=CR^2COOEt$ [32] that the conjugation of the group R^1 with the double bond increases the content of the hydrazone (in contrast to simple enamines[2,3,5]). The influence of β-substituents in enehydrazines is the same as in the enamines, i.e. electron-accepting substituents stabilise the enehydrazine. The influence of steric interactions of the substituents R^1 and R^2 in the strained planar structure



has been emphasised[33].

The results of a study[34] where it was shown in relation to the compound $R^1N(CH_3)NHC(CH_3)=CHCOR$ that an enhancement of the electron-accepting properties of the COR residue shifts the equilibrium towards the enehydrazine agree with the data for the influence of β-substituents. A study of the temperature dependence of the tautomeric equilibrium constant for the phenylhydrazone of acetoacetic ester[35] showed that the enehydrazine form is energetically more favourable (as should in fact be the case in the presence of an electron-accepting group in the β-position). The energy difference between the tautomeric forms, which is 2.5 kcal mole^{-1} in C_6D_5Br and 4 kcal mole^{-1} in DMSO, can be calculated from the temperature dependence of the composition of the tautomeric equilibrium mixture. In contrast to these data (as for the imine–enamine systems), in the absence of an electron-accepting group in the β-position, the hydrazone[36] or semicarbazone[37] form is energetically more favourable according to the results of quantum-chemical calculations (the Hückel method).

The shift to the enehydrazine form in DMSO compared with C_6H_5Br is consistent with data for the influence of the solvent (see Section II).[35] Overall, in the absence of electron-accepting substituents, hydrazones are more stable than the tautomeric enehydrazines, the difference in stability being greater than in an imine–enamine system[20,21,32].

IV. THE TAUTOMERISM OF CERTAIN ENAMINES WITH *N*-FUNCTIONAL GROUP SUBSTITUENTS

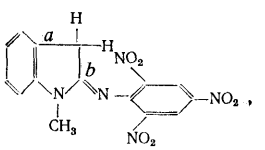
Few studies have been made on the tautomerism of the enamines $\diagdown\!\!\diagup C=C-NH-X$, where X = COR, SO_2, COOR, or another electron-accepting group. One of the first investigations demonstrated the occurrence of tautomerism in *N*-alkoxycarbonylimines[38]. The authors investigated vinylcarbamates $R-CH=CR^1-NH-COOEt$ by infrared spectroscopy and discovered a tautomeric equilibrium involving "iminourethanes" $R-CH_2-CR^1=N-COOEt$ [$R,R^1=(CH_2)_4$(a); $R,R^1=(CH_2)_5$(b); $R=H$, $R^1=C_6H_5$(c)]. The content of the enamide is 67–71% for compound (a), 60–68% for (b), and 31% for (c).

Despite this promising start to studies on the tautomerism of *N*-acylated imine–enamine systems, these data are not very trustworthy. Thus it has been shown[5] that the enamine $CH_3-CH=C(C_6H_5)NH_2$, unsubstituted at the nitrogen atom and having a structure similar to the enamine (*c*), exists in the enamine form to the extent of 92%, although the introduction of the electron-accepting group COOEt at the nitrogen atom should greatly displace the equilibrium towards the enamine, which follows from the analysis of all the available literature data and general considerations. Studies have been made recently[28] also on cyclic enamines analogous to compounds (a) and (b) with a t-butyl group at the nitrogen atom. Even in this instance the content of the enamine reaches 50%, so that it is altogether unlikely that the replacement of the electron-donating t-butyl group by the electron-accepting COOEt group gives rise to a very slight shift of the equilibrium towards the enamine form.

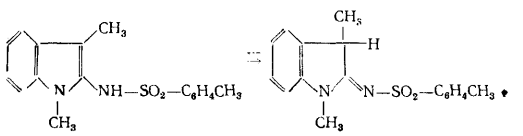
As will be shown below, the available literature data show on the whole that enamines with *N*-functional group substituents exist in the enamine and not the imine form, i.e. when groups of the type C=O, SO_2, and other electron-accepting substituents are present at the nitrogen atom, the enamine form is much more stable than the imine form.

For example, it has been shown[39] that nitriles, which do not have an α-hydrogen atom, combine with triethylsilane, giving rise to aldimines $R-CH=N-Si(C_2H_5)_3$ (R = t-C_4H_9 or C_6H_5). In the presence of an α-hydrogen atom aldimines rearrange almost wholly to the enamines $RR^1C=CHNHSi(C_2H_5)_3$.[40] When $R = R^1 = C_4H_9$, for example, the content of the imine form is only 4.

Interesting studies on indole derivatives have been made by Bailey and coworkers[41,42]. The imine structure has been found for *N*-methyl-2-(*N*-picrylamino)indole in the crystalline state[41]:

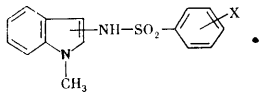


This was done in a fairly unusual way—by X-ray diffraction analysis involving a comparison of the bond lengths *a* and *b*; they are virtually the same (1.52 ± 0.005 Å). On the other hand, in solutions, this compound exists as an enamine (in different solvents). The same workers investigated also 1,3-dimethyl-2-tosylaminoindole, which exists in equilibrium with tosylimine[42]:

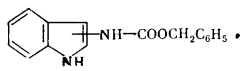


As for imine–enamine systems, in $CDCl_3$ this equilibrium is displaced towards the imine, while in DMSO it is displaced towards the enesulphamide.

The analogous 2- and 3-substituted indoles have been investigated[43,44]:

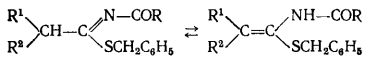


It was shown that the 3-substituted indole exists solely in the enesulphamide form, while the 2-substituted indole exists predominantly in the imine form. The equilibrium was found to be displaced towards the sulphonylimine when electron-accepting substituents X are introduced into the benzene ring. The sensitivity to this influence is small and independent of the solvent. In pure DMSO the content of the enesulphamide is higher than in the mixture of DMSO and 15% $CDCl_3$. *N*-Acyl-derivatives have been synthesised for comparison[43]:



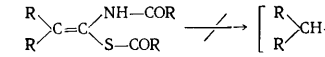
Regardless of the position of the substituent, these compounds exist solely as the enamides. The difference in the behaviour of 2- and 3-substituted enesulphamide isomers can be explained by the fact that the lone electron pair of the nitrogen atom in the α-position with respect to the sulphamide group in the 2-substituted isomer stabilises the sulphonylimine form; such stabilisation is impossible for the 3-substituted isomer. The above explanation has been confirmed by data[45] demonstrating the existence of the compound $R_2NC(CH_3)=NSO_2Ar$ (R_2N = morpholino) only in the form of the sulphonylimine.

α-Thio-substituted enamides have been studied in detail in a series of investigations by Walter and coworkers[46-48]. In contrast to the oxygen analogues iso-C_3H_7-$C(OCH_3)$=N-COR,[49] *N*-acyliminothioesters are in equilibrium with the enamides:



This is apparently due to the greater electron-donating capacity of the lone electron pair of the oxygen atom compared with that of the sulphur atom. The dependence of the equilibrium position on the nature of the groups R, R^1, and R^2 and on the solvent has been studied and the kinetics of the tautomerisation reaction have been investigated by ^{1}H NMR. The reaction was found to be of first order. Analysis of the authors' data leads to the following main conclusions: the change from R = CH_3 to R = C_6H_5 causes a very marked displacement of the equilibrium towards the *N*-acylimine form; electron-donating substituents in the β-position also stabilise the *N*-acylimine; DMSO in most cases causes a complete displacement of the equilibrium towards the enamide form relative to $CDCl_3$.

A further enhancement of the electron-donating properties of the α-substituent leads to a complete displacement of the equilibrium towards the *N*-acylimine. Thus acyliminodithioesters $C_6H_{11}CH_2C(SSR^1)$=NCOR exist entirely in the *N*-acylimine form[47]. The replacement of the cyclohexyl residue in the β-position by the phenyl group leads to the stabilisation of the enamine as a result of the conjugation of the double bond with the aromatic ring and the compound is the enamide $C_6H_5CH=C(SSR^1)NHCOR$. The replacement of the acyl group COR in this compound by the SO_2CH_3 residue leads to its complete conversion into the sulphonylimine $C_6H_5CH_2C(SSR)=NSO_2CH_3$ [47] (in agreement with the results of the study of Harmon and coworkers[43,44] on the relative stabilities of the enamide and enesulphamide systems). A weakening of the electron-donating capacity of the thio-group in the α-position destabilises the *N*-acylimine group and the ketene *S*,*N*-acylals are not converted into the tautomeric *S*,*N*-diacyliminothioesters[48]:



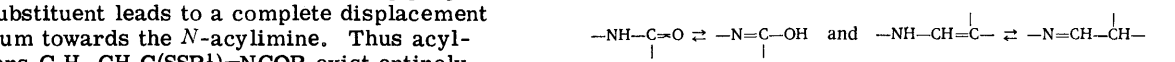
Thus one may conclude that the presence in the α-position of substituents exhibiting an appreciable +*C* effect (for example, OR, SR, and NR_2) is a necessary (but not sufficient!) condition for the appearance of the imine tautomers of enamides or enesulphamides.

V. CERTAIN APPROACHES TO THE PROBLEM OF THE ENAMIDE–*N*-ACYLIMINE TAUTOMERISM

As shown in the previous section, there have been rather few direct studies on enamide–*N*-acylimine tautomeric mixtures. On the other hand, this important problem is directly related to research fields such as transformations of antibiotics, the hydrolysis of peptides, transformations of optically active aminoacids, etc. In contrast to the enamine–imine tautomerism, the enamide–*N*-acylimine equilibrium is in most instances pseudomeric, i.e. is wholly displaced towards the enamide form. This hinders a direct study of the enamide–*N*-acylimine equilibrium and, on the other hand, justifies indirect approaches involving the acylation of tautomeric imine–enamine mixtures, the study of the reactivity of enamides, etc., which will be considered below.

The first major study on vinylcarbamates and vinylureas was published by Sato[50] as early as 1961. The study of the infrared spectra under different conditions led to the conclusion that vinylcarbamates unsubstituted in the α-position do not isomerise to *N*-acylimine, while α-substituted derivatives do isomerise. Such isomerisation of vinylureas proceeds even with the unsubstituted compounds and takes place very readily with α-substituted derivatives. A deficiency of Sato's study is that only infrared spectroscopy was used to demonstrate the structure; this method is not suitable, because the assignment of the bands in the range 1640–1700 cm^{-1} to the C=O, C=N, and C=C groups is fairly difficult for enamide–*N*-acylimine tautomeric systems and one is hardly justified in reaching any quantitative conclusions.

Ultraviolet spectroscopy has been used to study divinylurea $[(C_6H_5)_2C=CH-NH]_2CO$.[51] This compound has a maximum at 318 nm in the ultraviolet spectrum. When one of the nitrogen atoms is methylated, a 40 nm hyspochromic shift is observed, while methylation of both atoms entails a 51 nm hypsochromic shift, which the authors explain by the impossibility in the latter case of tautomerism of two types:



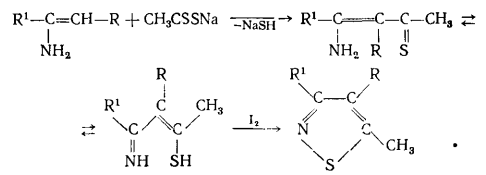
Analogous conclusions were also reached by the authors in the next investigation[52].

Here a small digression is necessary and the problem of the amide–imidol tautomerism as a possible alternative to the enamide–*N*-acylimine tautomerism must be touched upon. For saturated amides, such tautomerism is indeed sometimes observed if the imidol group is stabilised by substituent effects[53]. However, in the absence of such structural features calculation[54] indicates a much higher energy of the imidol form (by 15–20 kcal $mole^{-1}$), which

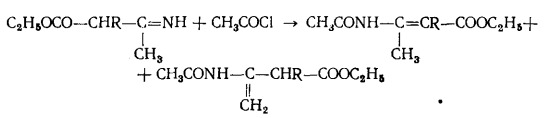
makes it possible to disregard it. So far there have been no comparative calculations of the energies of the *N*-acylimine and imidol forms and our recent calculation[55] for the tautomers $CHCl_2-CH=N-COCH_3$ and $CCl_2=CH-N=C(OH)-CH_3$ showed that the *N*-acylimine form is energetically more favourable than the imidol form to the extent of 16 kcal mole^{-1}.

Goszczynski and Zielinski[56] investigated the acid hydrolysis of *N*-styrylacetamides $CH_3-CO-NH-CR=CR^1-Ar$; it has been shown by infrared spectroscopy that in the protonated form these compounds are *N*-acylimine tautomers $CH_3-CO-NH=CR-CHR^1-Ar$. A similar fact was noted also in an earlier study of the oxidation of imine–enamine systems[57], where it was shown that, when salts are formed, both imines and enamines give rise to imine salts†.

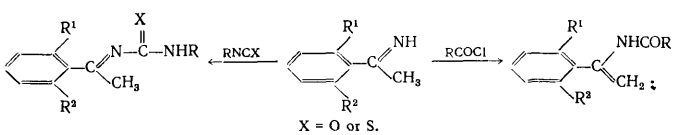
The problem of the enamide–*N*-acylimine tautomerism has also been studied by investigating the acylation of imine–enamine tautomeric mixtures. Such studies were published ten years ago, that of Crenshaw et al.[58] on the thioacetylation of enamines being one of the first. By oxidising with iodine the product of the interaction of CH_3CSSNa with the enamine, the authors were able to isolate an isothiazole, which is formed via the following mechanism according to their view:



When cyclohexanone and isobutyral imines are acylated by acyl chlorides, isocyanates, and isothiocyanates,[59] the products are the tautomeric enamides or enethioamides and not *N*-acylimines. When the $H_2NCR=CR^1R^2 \rightleftarrows HN=CRCHR^1R^2$ tautomeric mixture is acylated, only the enamide is again formed[6]. Attempts have likewise been made to obtain *N*-acylimines by acylating imines. For aliphatic imines, such an attempt was unsuccessful—the authors[60] obtained the two isomeric enamides:

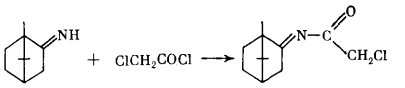


The reactions of acetophenone imines with isocyanates or isothiocyanates yielded *N*-acylimines, while those with acyl chlorides gave enamides[61]:

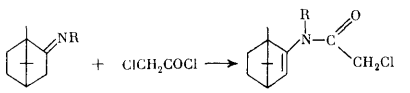


X = O or S.

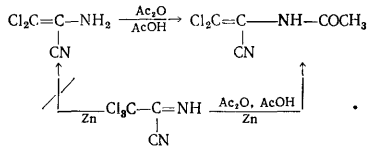
The yield of the *N*-acylimine increases with increasing branching of the substituents R^1 and R^2. *N*-Acylimines are formed more readily by reaction with isocyanate than by reaction with isothiocyanate. Thus, for $R^1 = R^2 = CH_3$, treatment with RNCS yielded the enamide, while treatment with RNCO gave rise to the *N*-acylimine. The *N*-acylimine was also obtained by reaction with chloroacetyl chloride[61]:



The stability of the *N*-acylimine is in this case apparently related to the greater stability of the exocyclic double bond, although in principle the double bond can be converted into a ring[61]:



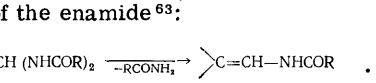
The following transformations have been described in connection with a study of chloral derivatives[62]:



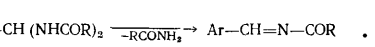
Evidently, both the enamine and imine give rise to β,β-dichloro-α-cyanovinylacetamide.

Thus *N*-acylation of enamines always results in the formation of enamides, while *N*-acylation of imines sometimes gives rise to *N*-acylimines, although the tautomeric enamides are again more frequently produced.

The greater stability of the enamide form compared with the *N*-acylimine form may be inferred also from the results of the elimination of amides from alkylidenebisamides.[63,64] If there is a hydrogen atom in the β-position relative to the amido-group, the elimination proceeds with formation of the enamide[63]:

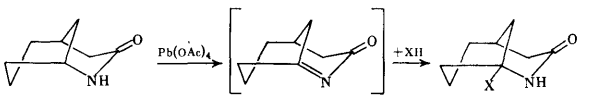


If such a hydrogen atom is absent, the elimination process proceeds under more severe conditions and *N*-acylimines are formed[64]:

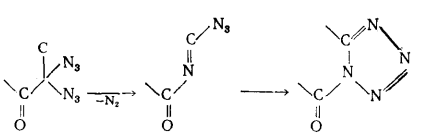


Studies which demonstrated the formation of an unstable tautomeric *N*-acylimine form as the reactive intermediate belong to another series of investigations associated with the problem of the enamide–*N*-acylimine tautomerism. Almost all studies in this group have been carried out in the last five years.

For example, the oxidation of a bicyclic lactam proceeds via the *N*-acylimine[65]; the intermediate *N*-acylimine readily combines with nucleophiles:

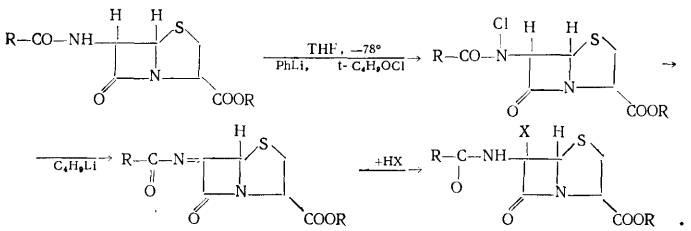


Many photochemical reactions of amides[66] and azidoketones[67,68] involve the formation of intermediate *N*-acylimines. The *N*-acylimines formed in the reaction can readily combine with alcohols[66], can be isolated in a free state[68], or, as in the case of diazidoketones, are converted into tetrazoles[67]:



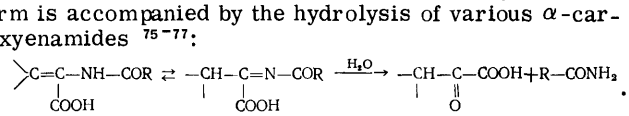
†However, one should bear in mind that the same cation is obtained on *N*-protonation of the *N*-acylimine form and on *C*-protonation of the enamide, so that in this sense the problem of the tautomerism of the initial compounds remains open.

The formation of *N*-acylimines from saturated amides was demonstrated in studies [69,70] where an amide containing a hydrogen atom in the α-position was acted upon by t-butyl hypochloride and an alcohol was then made to add to the *N*-acylimine formed on dehydrochlorination. Using this method, Firestone and Christensen [71] introduced various functional groups in the $C_{(6)}$ position in penicillin:

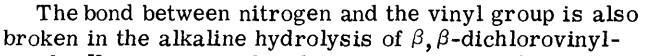


It may be that a study of such reactions will assist a deeper understanding of the metabolism in the living cells of penicillin-based preparations.

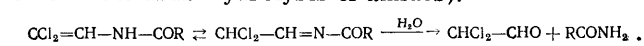
According to the results of Morin and coworkers [72-74], the thermal and catalytic expansion of five-membered O- and S-containing lactams proceeds via the *N*-acylimine form. The formation of the intermediate *N*-acylimine form is accompanied by the hydrolysis of various α-carboxyenamides [75-77]:



The bond between nitrogen and the vinyl group is also broken in the alkaline hydrolysis of β,β-dichlorovinylamides [78]: consequently, the reaction proceeds via the *N*-acylimine form (since the nitrogen–carbonyl bond is broken in the usual hydrolysis of amides):

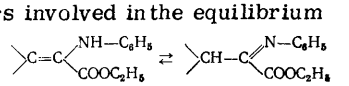


In those cases where the enamide and *N*-acylimine forms lead to different products, it is not difficult to establish the involvement of the *N*-acylimine tautomeric form in the reaction. The situation is more complex when both forms give rise to identical products, for example:

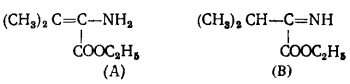


The occurrence of tautomerism in β,β-dichlorovinylamides or their derivatives has been suggested in a number of studies [78-81], but nucleophilic addition to β,β-dichlorovinylamides has been studied quantitatively only recently [82-84]. That the reaction proceeds via the *N*-acylimine form is indicated by data concerning the influence of the catalyst concentration and substituents on the rate of reaction, the presence of the kinetic isotope effect, the reactions with model secondary enamides, etc. The study of the kinetics of the addition of alcohols to *N*-acylimines using the reactions of alcohols with *N*-acylchloral imines, [85] as well as quantum-chemical calculations for individual tautomeric forms and the corresponding common anions [55] made it possible to estimate the tautomeric equilibrium constants (5.7×10^{-4}), the energy difference between the two forms (5 kcal mole^{-1}), and the influence of substituents on the equilibrium position. Electron-donating substituents tend to shift the equilibrium towards the *N*-acylimine form, which agrees well with data for simple imine–enamine systems without a hydrogen bond [4,12,14-16].

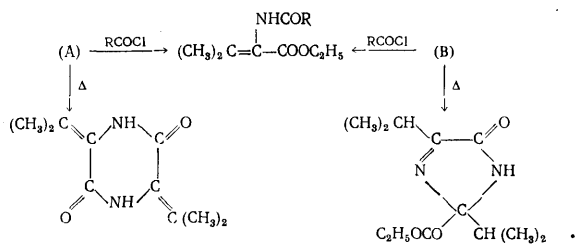
Shin and coworkers [86-90] studied α,β-unsaturated acids and their esters involved in the equilibrium



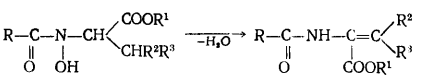
It is of interest that there is no such equilibrium for the analogue unsubstituted at the nitrogen atom—both forms exist individually:



The compounds (A) and (B) give rise to a single enamide on acylation (cf. Refs. 6 and 59) and to different condensation products on heating:

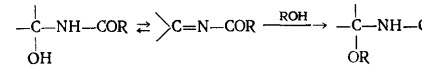


The same workers [87-90] found that, instead of the expected *N*-acylimines, their more stable tautomers (enamides) are formed on dehydration of *N*-substituted α-carboxy-*N*-hydroxyamides:

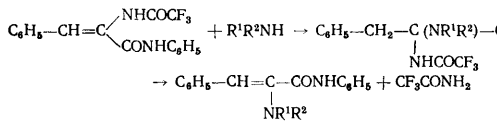


Isomerisation proceeds more readily for $R^2 = H$ than for $R^2 = OCH_3$. [90] This agrees with the general postulate that any electron-accepting influence stabilises the enamine.

Nucleophilic substitution in the α-position of an *N*-substituted enamide also proceeds, according to Meyers and Shaw [91], via the *N*-acylimine (elimination–addition):



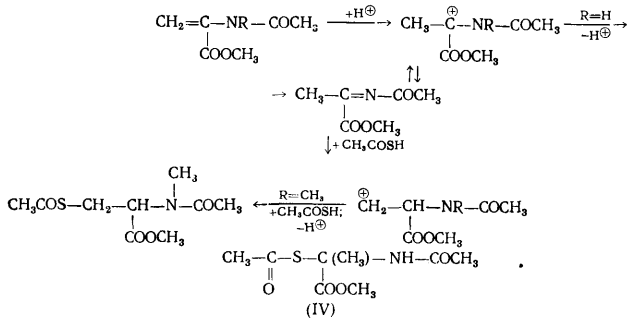
The reactions of a series of α-substituted enamides $C_6H_5CH{=}C(CONHR)NH{-}COR^1$ with mercaptans, amines, and hydrazines were studied recently [92]. The addition proceeds in accordance with the Markovnikov rule; in the case of amines and hydrazine, the reaction continues further:



For hydrazine, the hydrazone form $C_6H_5{-}CH_2{-}C(CONHC_6H_5){=}N{-}NH_2$ is more stable. The formation of the transamination product as a result of addition–elimination has been demonstrated by the absence of reaction for saturated analogues. The authors believe [92] that the addition takes place at the C=N bond of the *N*-acylimine tautomer, because they claim that the addition to the C=C bond of the enamine should proceed contrary to the Markovnikov rule because of the polarisation of the C=C bond under the influence of the carbonyl group. However, the *N*-acylimine form cannot be detected by spectroscopic methods [92].

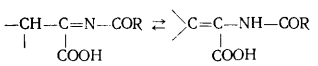
The literature data on *N*-acylimines as the reactive intermediates in the reactions of α-carboxylated enamides have been surveyed to some extent in a brief report [93], which also describes a study of the interaction of α-methoxycarbonyl-enamides with thioacetic acid. The mode of

addition is different for compounds with an NH group and for the *N*-methylated compound. The authors[93] suggest the following reaction mechanism:



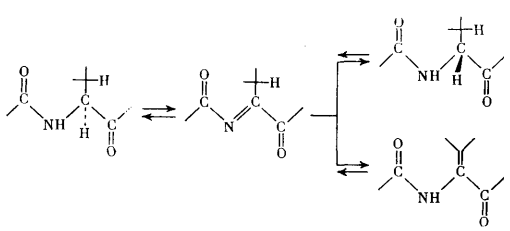
The exchange of the thioacetate group in compound (IV) for the OCH_3 group as well as the reduction of (IV) to $CH_3OCS-CH(CH_3)-NH-COCH_3$ apparently proceed similarly[93].

Studies in which the problem of the enamide–*N*-acylimine tautomerism is considered in relation to the structures of antibiotics, peptides, and optically active aminoacids are of very great interest. Bycroft[94] noted the great importance of the following processes in living organisms:



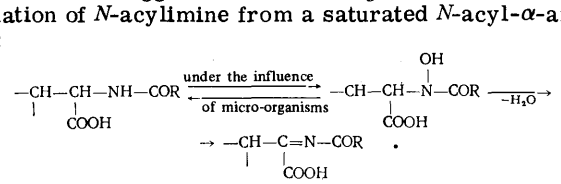
(11)

In particular, Bycroft explains the presence of racemates of aminoacid derivatives in organisms. Since the peptides in living cells are made up of L-aminoacids, D-aminoacids are apparently formed via reversible oxidation-reduction involving *N*-acylimine:



As shown in the scheme above, it may be that the intermediate *N*-acylimine is converted into an enamide. The mechanism illustrated in the above scheme is confirmed by the absence of the D-configuration from the *N*-methylaminoacids, which frequently form part of antibiotics, and by the presence in many peptides of α,β-unsaturated *N*-acyl-α-aminoacids, formed as the tautomers of *N*-acylimines. The above scheme also explains the α-epimerisation rule: if the aminoacid contains more than one chiral centre, the configuration is inverted only at the α-carbon atom. Only one point remains obscure in this scheme—namely why an oxidation–reduction equilibrium occurs at all and what reagents cause it to be established.

Some light has been thrown on this problem by studies[95,96] whose authors suggested the following mechanism for the formation of *N*-acylimine from a saturated *N*-acyl-α-aminoacid:



α-Aminoacids, *N*-acyl-α-aminoacids, and their derivatives $>CHC(COOR)=NR$ and $>C=C(COOR)NHCOR$ have been obtained[96] by a method analogous to that in Refs. 68 to 70. It is seen that here too acylation of imines gives rise to the tautomeric enamides.

Recently there has been a particular growth of interest in α-carboxyenamides (*N*-acyldehydroaminoacids) when it has become clear that they are the starting compounds in the synthesis of peptides[97] and in addition are components of natural peptides[98]. The overall mechanism of the reactions of *N*-acylaminoacids in organisms is as follows[95]: initially biological *N*-hydroxylation and dehydration lead to the *N*-acylimine; in the presence of proton-containing nucleophiles they then rapidly add to the C=N bond, while in the absence of such bonds *N*-acylimines rapidly rearrange to α-carboxylenamides. The addition of peptide residues to the latter also apparently proceeds via the *N*-acylimine form, because the mode of addition is inconsistent with the polarisation of the double bond under the influence of the carboxy-group.

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