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An account of the chemistry of 3,4-disubstituted-5-isoxazolones+

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Abstract

The course of chemical reactions such as oxidation, alkylation, Michael addition and hydrogenolysis in tautomers of 3,4-disubstituted-5-isoxazolones has been presented. Convenient syntheses of 3-alkyl-4-arylmethyl (and branched arylmethyl)-5(2H)-isoxazolones and the methods for incorporating isoxazole ring in new bicyclic systems have been highlighted. Reactions of title compounds with reducing enzymes as the subject of future study has been suggested.

Key words: 4-Arylmethylene-5(4H)-isoxazolones, 4-arylmethyl-5(2H)-isoxazolones, oxidation, alkylation, Michael reaction, hydrogenolysis, ring expansion, ring contraction.

An important factor of any drug developmental activity is devising a cost-effective synthetic strategy which would inspire not only to provide the desired compound in minimal number of steps and in optimal yields but also to provide methods for preparation of their analogs and homologs for exploratory research activity. Heterocycles constitute the major share of the synthetic drugs and a search for new heterocyclic drug is often confronted with the problem of tautomerism because the exact population of tautomers at the active site is difficult to ascertain. One of the possible ways to overcome this problem is to synthesize compounds which specifically represent only one tautomer and are incapable of equilibrating to the other possible tautomers. The prerequisite for this strategy is the complete understanding of the chemistry of the desired heterocycle. One such heterocycle which acquired considerable attention in our laboratory for its pregnancy-interceptive activity at uteroplacental junction is 3,4-disubstituted-5-isoxazolone. This class of compounds did not exhibit estrogenic, antiestrogenic, progestational or antiprogestational activity in experimental animals. The mechanism of pregnancy-interceptive activity and the structure-to-activity relationship of different tautomers are therefore subjects of considerable interest. The present account describes the chemistry of this class of compounds and highlights the course of reactions in various tautomers.

Detailed understanding of the tautomerism in 3,4-disubstituted-5-isoxazolones, first reported by Kohler and Blatt in 1928[1], came from the work of Katritzky in 1961[2]. He clearly

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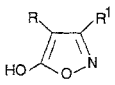
demonstrated the presence of three tautomeric forms which, for the sake of simplicity, are described as the CH or 4H form (I), the NH or 2H form (II) and the OH form (III) (Fig. 1).

I
CH or 4H form

II
NH or 2H form

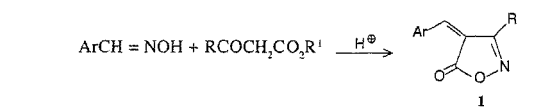


III
OH form

FIG. 1.

The characterization of these tautomers has been rationalized on the basis of the IR spectra of their derivatives[2]. The characteristic carbonyl absorption band in the IR spectrum of 5(2H)-isoxazolone derivatives ranges between 1670 and 1720 cm^{-1}, while the same absorption band in 5(4H)-isoxazolone derivatives appears between 1790 and 1810 cm^{-1}. The interconversions of the CH and the OH forms are possible because of a direct sigmatropic effect, while the interconversions of any of these forms to NH form may possibly proceed through intermolecular proton transfer[3]. The stability studies[2-7] of these tautomers in various solvents have also furnished interesting results. For example, in low-polarity solvent (deuteriochloroform) the CH form is predominant, while in more polar solvent (deuteriodimethylsulphoxide) the NH form is more pronounced. In strongly basic medium possibly the OH form is the main tautomer. These observations, therefore, suggest a re-examination of results recorded before 1961 and also indicate careful analysis of the course of chemical reactions in this class of compounds.

Our studies on the chemistry of 5-isoxazolones started with the synthesis of 3-methyl-4-arylmethylene-5(4H)-isoxazolone (**1**), the first model compound selected for evaluating its pregnancy-interceptive activity. A convenient approach for obtaining this class of compounds suggests utilization of **1** as the starting material which in turn can be easily prepared by reacting substituted benzaldoxime with β-ketoester (Scheme 1)[8-14].



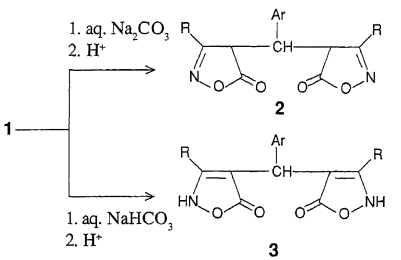
1

SCHEME 1.

In principle, hydride attack on **1*** should be regioselective since the arylmethylene bond is in conjugation with C=N and C=O groups. The hydride attack on the arylmethylene carbon in **1** may then lead to either CH or NH or both the tautomers of the 3-alkyl-4-arylalkyl-5-isoxazolones. In the light of these possibilities, it was considered desirable to ascertain the

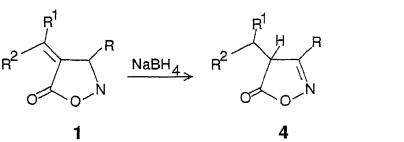
* For the sake of simplicity the details of substituents (R, Ar, etc.) in all schemes have not been furnished since they do not influence the chemistry of isoxazolones. However, the general formula may be represented as 3-alkyl-4-arylalkyl-5-isoxazolones.

course of reaction after the nucleophilic attack (other than the hydride) on arylmethylene carbon in **1**. For example, the reaction of **1** with aq. sodium carbonate, studied by earlier workers[8], do confirm the regioselective nucleophilic attack for the formation of **2** (Scheme 2). However, in this case, the other possible structure (**3**) was not ruled out. This led to a reinvestigation[15] and on the basis of carbonyl absorption band between 1660 and 1690 cm^{-1} in the IR spectrum and the appearance of the arylmethine proton at δ 4.76 in the PMR spectrum, the correct structure of **2** was assigned as **3**.



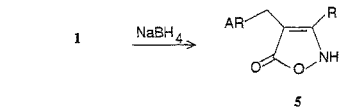
SCHEME 2.

Similar was the observation for the course of sodium borohydride reductions in compounds structurally related to **1**. For example, Beccalli *et al*[16] in 1988 assigned the structure of sodium borohydride reduction products of 4-arylmethylene- and 4-alkylidene-5(4H)-isoxazolones as **4** (Scheme 3) but the reported IR signals for the carbonyl absorptions (1680–1690 cm^{-1}) raised doubts for the assigned structures. A similar investigation[15] carried out later indicated that the borohydride reduction of **1** exclusively gave **5** as was evident



SCHEME 3.

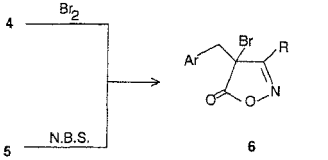
from the IR carbonyl absorption bands between 1660 and 1690 cm^{-1}, and from the PMR signal of the arylmethyl protons which instead of a doublet appeared as a singlet. A convenient method for the preparation of our model compound, namely, 3-alkyl-4-arylmethyl-5(2H)-isoxazolone was thus achieved (Scheme 4).



SCHEME 4.

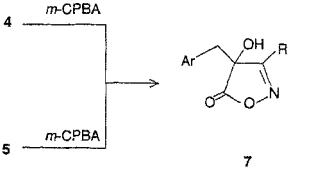
The chemistry of 3-alkyl-4-arylmethyl-5(2H)-isoxazolones was expected to be interesting since their structures represent cyclic enaminones and under various reaction conditions the possibility of their equilibration to other tautomers existed. In a situation such as this, studies on the course of alkylation and oxidation reactions become more attractive. It may be reasoned that alkylation of 3-alkyl-4-arylmethyl-5(2H)-isoxazolones may lead to N–C- and/or O-alkyl derivatives and the oxidation of 5(2H)-isoxazolone derivatives to N–N, N–C, C–C, N–O and/or O–O dimers. Similarly, free radical reactions may help to create linkages through either carbon or nitrogen atom. The results of the investigations are as follows:

The reaction of compound **5** with N-bromosuccinimide yielded the 4-bromo derivative (**6**) (Scheme 5)[15]. The same product (**6**) was also obtained by reacting 4-arylmethyl-5(4H)-isoxazolone (**4**) with bromine[17].



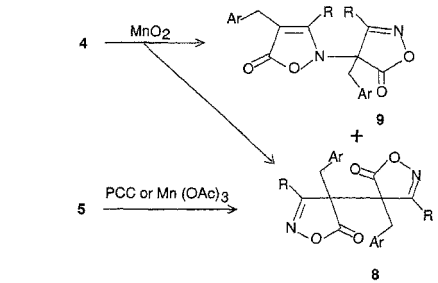
SCHEME 5.

Oxidation of compounds **4** and **5** with *meta*-chloroperbenzoic acid (*meta*-CPBA) is reported[18,15] to furnish compound **7** (Scheme 6). Oxidation of compound **4** with MnO_2 has



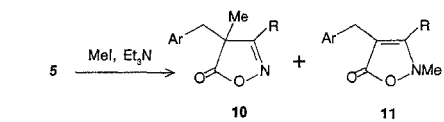
SCHEME 6.

been reported[19] to furnish a mixture of C–C and C-N-linked dimeric products (8 and 9) (Scheme 7), while the oxidation of compound **5** with pyridinium chlorochromate (PCC) or manganic acetate gave the C–C-dimerised product **8** (Scheme 7)[15].



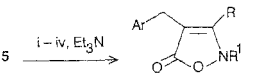
SCHEME 7.

Alkylation of 3,4-disubstituted-5-isoxazolones with diazomethane[2, 5, 20, 21] or alkyl halides[1, 20] has been reported to yield N- and/or O-alkylated products. These results are not completely satisfactory since ^{13}CNMR evidence for the presence of reasonable percentage of CH form demands the formation of C-alkylated products. Detailed studies[22] on the alkylation reactions of 3-alkyl-4-arylalkyl-5(2H)-isoxazolones carried out recently gave interesting results. For example, alkylation of compound **5** with methyl iodide in the presence of triethylamine gave the 4-methyl (**10**) and the 2-methyl (**11**) derivatives (Scheme 8). This is the first report of C-



SCHEME 8.

alkylation in 5(2H)-isoxazolones. The structural assignment of C-alkylated derivative (**10**) was made on the basis of IR, PMR and ^{13}CNMR spectra. As would be expected the reaction condition influenced the formation of C-substituted product[23]. For example, alkylation in the presence of methyl iodide and triethylamine at higher temperature or the use of 4-dimethylaminopyridine (DMAP) as catalyst invariably led to N-alkylated product **11**. The nature of the alkyl halide also governed the course of the reaction. Except methyl iodide, other alkyl halides such as ethyl, butyl- or amyl halides gave only N-alkylated derivatives (**12–14**) (Scheme 9) but the reactions with propargyl[23] and allyl halides[24] furnished C- and N-alkylated derivatives (**15, 16**) (Scheme 10). Michael reaction of compound **5** also gave C- and N-alkylated derivatives[22]. Reactions of compound **5** with acrylonitrile or ethyl acrylate in the presence of triethylamine besides furnishing N-substituted derivatives (**18, 20**) yielded respectable quantities of C-alkylated products (**17, 19**) (Scheme 10). Similar reactions with methyl vinyl ketone resulted in almost quantitative yields of C-substituted product (**21**). Unlike these alkylation reactions the acylation and aroylation of 5(2H)-isoxazolones **5** exclusively furnished the N-substituted derivatives (**23–25**)[25] (Scheme 9).



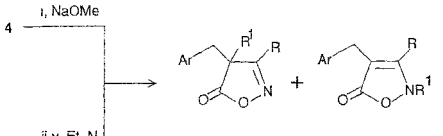
Refs 23 & 25

12–14, 23–25

i. EtBr ii. BuBr
iii. AmI iv. PhCOCl
v. $MeCo_2Cl$ vi. MeCOCl

Compound no.	R^1
12	Et
13	Bu
14	Am
23	COPh
24	CO_2Me
25	COMe

SCHEME 9.



Ref. 24

15, 17, 19, 21 **16, 18, 20, 22**

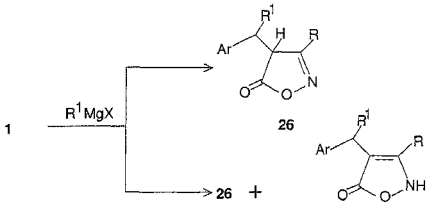
Refs 22, 23

i. X $CH_2CH{=}CH_2$ ii. $BrCH_2C{\equiv}CH$
iii. $CH_2{=}CHCN$ iv. $CH_2{=}CHCO_2Et$
v. $CH_2{=}CHCOMe$

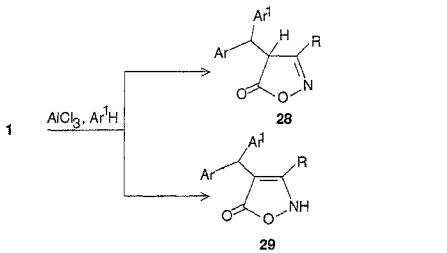
Compound nos	R^1
15–16	$CH_2CH{=}CH_2$ or $CH_2C{\equiv}CH$
17–18	CH_2CH_2CN
19–20	$CH_2CH_2CO_2Et$
21–22	CH_2CH_2COMe

SCHEME 10.

It may be concluded from the observations recorded in the preceding text that a hydride attack on the arylmethylene carbon in compound **1** predominantly yields 5(2H)-isoxazolone which could then be used for building C–C linkages at C-4 in 3-alkyl-4-arylmethyl-5(2H)-isoxazolones (**5**). This conclusion strongly suggests that direct alkylation of arylmethylene carbon in compound **1** should be possible and it should furnish branched 4-arylalkyl-5(2H)-isoxazolones. Grignard reaction of compound **1** has been reported to yield 5(4H)[26,27] and a mixture of 5(4H)- and 5(2H)-isoxazolones[15] (Scheme 11). Similarly, direct arylation of the arylmethylene carbon in compound **1** has been accomplished by reacting it with substituted benzenes in the presence of anhydrous $AlCl_3$[27]. In this reaction also the products have been described as 5(4H)-isoxazolones (**28**) and 5(2H)-isoxazolones (**29**)[28] (Scheme 12). The possibility of elaboration of the arylmethylene carbon in compound **1** has been achieved by

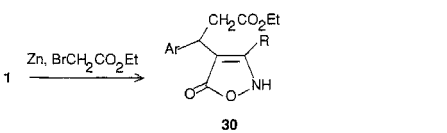


SCHEME 11.



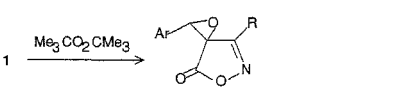
SCHEME 12.

carrying out Reformatsky reaction[29]. In this case, the product has been identified as 5(2H)-isoxazolone derivative (**30**) (Scheme 13). Direct functionalization of arylmethylene carbon



SCHEME 13.

has been made possible by reacting compound **1** with tert-butyl hydroperoxide (Scheme 14)[30]. The resulting epoxide (**31**) may react with nucleophiles to yield interesting compounds.

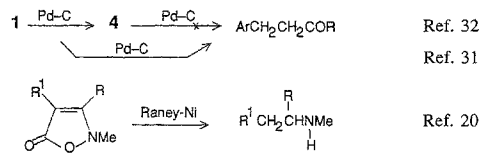


SCHEME 14.

Convenient methods of syntheses for obtaining branched 4-arylalkyl-5(2H)-isoxazolones and 4,4-disubstituted-5(2H)-isoxazolones laid the foundation for understanding studies on the ring contraction, ring expansion and for incorporating isoxazole ring in bicyclic systems. Strategies for the desired synthesis of attaining these objectives can be designed if only the course of reaction leading to the cleavage of –CO–O– and/or N–O bonds are known (Fig. 2).

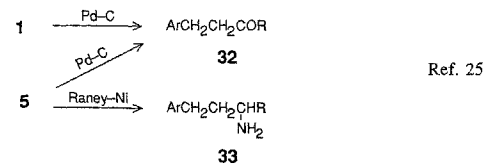
FIG.2.

This prompted the studies on hydrogenolysis and hydride reductions of various 5-isoxazolone derivatives. Failures and success of N–O cleavage during hydrogenolysis are recorded in literature[20,31-34]. For example, 3-alkyl-4-aryl-methyl-5(2H)-isoxazolone are reported not to undergo hydrogenolysis[31] in the presence of Pd-C, while other workers indicated smooth cleavage of N–O bonds in 3,4-disubstituted-5-isoxazolones during hydrogenolysis in the presence of Pd–C[34] or Raney–nickel[33]. The products of successful hydrogenolysis were either ketones or secondary amines (Scheme 15). Contrary to the earlier report[31], it was found



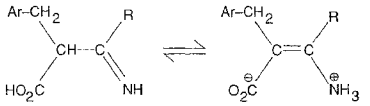
SCHEME 15.

later[25] that all 3-alkyl-4-arylmethylene-5(4H)-isoxazolones and 3-alkyl-4-arylmethyl-5(2H)-isoxazolones do undergo hydrogenolysis in the presence of Pd–C to yield 4-aryl-2-butanones (**32**) (Scheme 16). The 3-alkyl-4-arylmethyl-5(2H)-isoxazolone in the presence of Raney–Ni furnished 4-aryl-2-butanamines (**33**) (Scheme 16). The reaction pathway for the hydrogenolysis



SCHEME 16

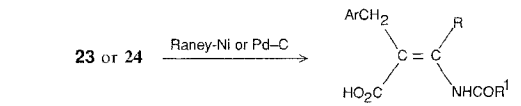
products envisages[31] the formation of the β-iminobutyric acid (IV) as the labile intermediate (Fig.3).



IV V

FIG. 3.

The evidence to this envisaged pathway was obtained later[25]. It was found that the hydrogenolysis of 2-benzoyl- and 2-carbomethoxy-3-alkyl-4-arylmethyl-5(2H)-isoxazolones (**23, 24**) in the presence of Raney–Ni or Pd–C furnished 2-arylmethyl-3-benzoylamino-2-butenoic acid (**34**) and 2-arylmethyl-3-carbomethoxy amino-2-butenoic acid (**35**), respectively (Scheme 17). Oxidation[35] of these butenoic acids with hydroxy tosyloxyiodosobenzene (HTIB) yielded oxazoles (**36**)



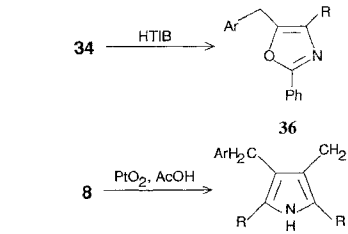
34–35

Ref. 25

Compound no.	R^1
34	Ph
35	OMe

SCHEME 17.

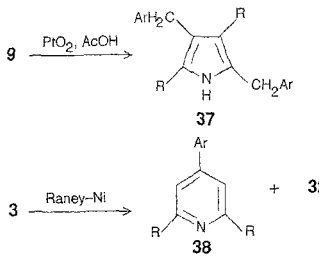
(Scheme 18). An interesting transformation of isoxazole to oxazole was thus achieved. Studies on the hydrogenolysis also helped to transform isoxazolones to pyrroles[19] and pyridines[25] (Scheme 18). For example, hydrogenolysis of dimeric isoxazolones (**8, 9**) in the presence of PtO_2 in acetic acid furnished pyrroles (**37**). Ring expansion of



36

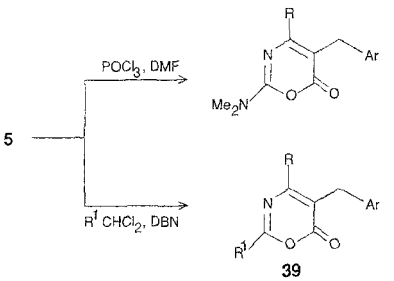
Ref. 35

Ref. 19



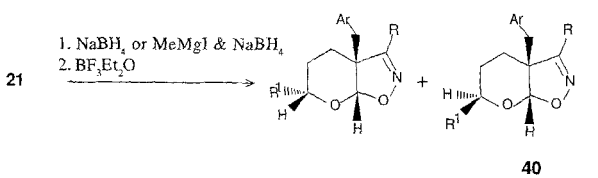
SCHEME 18.

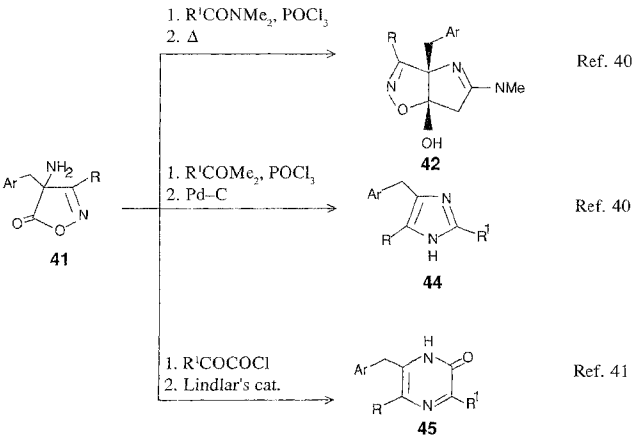
isoxazolones to pyridines occurred during the hydrogenolysis of compound **3** in the presence of Raney–Ni. A facile ring expansion of isoxazolones to oxazinones (**39**) has been reported[36–39] (Scheme 19).



SCHEME 19.

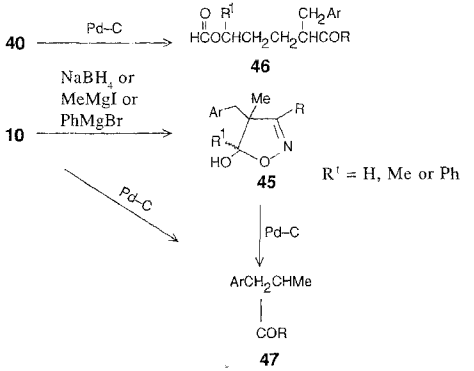
Exploration of reactions for incorporating isoxazole ring in bicyclic systems rests on the choice of 4,4-disubstituted-5-isoxazolones. For example, the 4,4-disubstituted-5(4H)-isoxazolone (**21**) could be smoothly converted to pyrano [3,2-d] isoxazoles (**40**)[22], while the ring closure[40] of 4-amino-4-arylalkyl-5(4H)-isoxazolone (**41**) led to pyrrolo [2,3-d] isoxazolone(**42**)



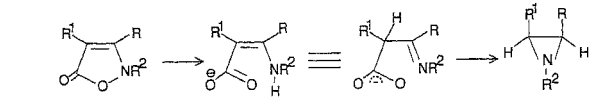


SCHEME 20

(Scheme 20). In both the cases the stereochemistry of the ring junction was *cis*. Another interesting utility of amine (**41**) has been demonstrated for the ring expansion of the isoxazolone ring to pyrazinones (**43**)[41] and its transformation to imidazoles (**44**)[40].

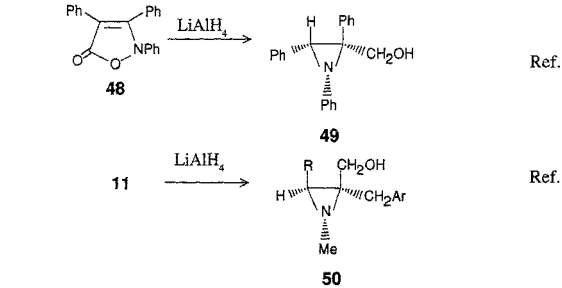


SCHEME 21.



SCHEME 22.

Pyrano [3,2-d]-isoxazoles are good substrates for understanding the N–O cleavage during hydrogenolysis. It may be argued that fascile N–O cleavage in 5-isoxazolones may owe its origin to the carbonyl group present at position 5 of the heterocyclic ring. Pyrano [3,2-d]-isoxazoles and their precursor lactols (45)[42-43] are, therefore, important substrates for studying their hydrogenolysis products. The products (**46**, **47**) of hydrogenolysis of compounds **40** and **45** (Scheme 21)[23] have clearly demonstrated that the cleavage of the N–O linkage does not require a carbonyl group at position 5 in isoxazolones. Ring contraction of the isoxazolone is also possible if N–O cleavage is carried out in a manner so as to facilitate the attack of iminine nitrogen on C-4 (Scheme 22). Such a ring contraction was observed during the reduction of 2,3,4-triphenyl-5(2H)-isoxazolone (**48**) with lithium aluminium hydride to yield aziridine (**48**) (Scheme 23)[44]. It was suggested that interaction occurring between the HOMO



SCHEME 23.

of the N–O bond and LUMO of the enolate bond gave rise to 1,3-sigmatropic migration of N-atom to furnish the aziridines. However, this solitary report had two limitations. Firstly, it did not indicate the general applicability of the reaction and secondly it did not comment on the possibility of predicting the stereochemistry of the resulting aziridine. Answers to these questions came later[45]. It was found that the substituent at C-3 of isoxazolone ring invariably orients itself *cis* to the CH_2OH group which owed its origin to the carboxylate linkage of the isoxazolone ring. These results indicated that ring rotation occurred during skeletal rearrangement of isoxazolone around C-3 and C-4 bonds (Fig. 4). The orientation of other groups in the aziridine was possibly governed by the steric bulk of the substituents.

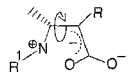


FIG. 4.

It may be concluded that the structural assignments of the reaction products 3,4-disubstituted-5-isoxazolones should be carefully made. The extreme susceptibility of this class of compounds towards hydrogenolysis can help to obtain open chain compounds which are otherwise difficult to obtain. An interesting future studies on the chemistry of 3,4-disubstituted-5-isoxazolones would be their reactions with reducing enzymes both in aqueous and organic solvents.

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