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A SIMPLE SYNTHETIC METHOD OF CYCLOALKAISOXAZOLES

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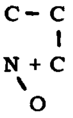
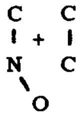
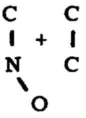
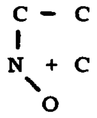
Various synthetic methods of isoxazole derivatives have extensively been investigated and excellent reviews of them were recently given by A. Quilico[1] and N. K. Kochetkov and S. D. Sokolov[2].

The synthetic plans of isoxazole ring can be reduced to the following three different schemes indicated by I, II, and III.

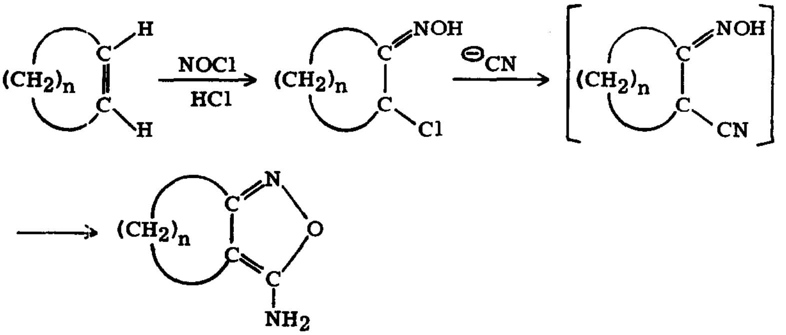

(I)


(II)


(III)


(IV)

During the investigation of displacement reaction of α-chlorocycloalkanone oxime with nucleophilic reagents, we have found a new synthetic method of cycloalkaisoxazole derivatives which is different from any method mentioned above, and expressed in the following successive formulae or fundamentally indicated by IV.



The reaction of α-chlorocyclohexanone oxime[3)] with potassium or sodium cyanide in dimethylsulfoxide or ethanol afforded a colorless crystalline material, in 48% yield, m.p. 117 ~ 118°C, recrystallized from a mixed solvent of ether and petroleum ether.

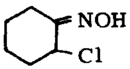
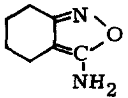
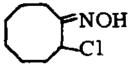
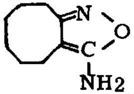
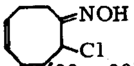
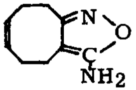
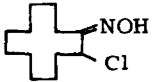
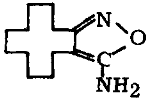
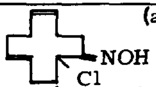
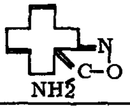
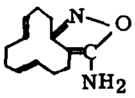
The structure has been assigned to be 3-amino-4, 5, 6, 7-tetrahydrocyclohexa [C] isoxazole from its elemental analysis, infrared and ultraviolet spectra (Calcd. for $C_7H_{10}N_2O$: C, 60.85 ; H, 7.30 ; N, 20.28. Found : C, 61.19 ; H, 7.42 ; N, 20.23. I. R., primary amino group at 3310 ~ 3160 cm^{-1} and a conjugated system, -N=C-C=C- at 1655 cm^{-1} and 1500 cm^{-1}. U. V. λ_{max}^{EtOH} , 243 mμ , ε = 7,400).

Furthermore, umambiguous proof of the structure was achieved by the comparison of the melting point and infrared spectrum with those of an authentic sample[4)], which was obtained from the reaction of α-cyanocyclohexanone[5)] with hydroxylamine.

The formation of isoxazole ring may easily be understood from displacement of active chlorine atom with cyanide anion followed by instantaneous ring closure between oximino group.

This method was extended to α-chlorocyclooctanone oxime,

TABLE I

cyclo-alkene	α-chloro-oxime (yield %)	3-aminocycloalka [C] isoxazole					
			yield (%)	m.p. (^{o}C)$^{(b)}$	UV (mμ)	IR (cm^{-1})	
cyclo-hexene	 (90 - 95)		48	117 - 118	243 (ε, 7400)	3310 3160	1655 1640 1500
cyclo-octene	 (90 - 95)	 *	96	77 - 78	252 (ε, 9700)	3380 3210	1650 1610 1500
cyclo octadiene	 (80 - 90)	 *	89	81.5 - 82.5	251 (ε, 8230)	3310 3180	1645 1610 1500
cis-cyclo-dodecene	 (80)	 *	95	119 - 121	253 (ε, 7960)	3430 3280 3120	1650 1610 1495
cis, trans, trans-1, 5, 9-cyclo-dodecatriene	(a)  (90 - 95)	 *	95	148 - 150	244 (ε, 8000)	3420 3310 3180	1645 1615 1500
trans, trans, trans-1, 5, 9-cyclo-dodecatriene	 (90 - 95)	 *	90	131 - 134	256 (ε, 7900)	3420 3310 3180	1645 1615 1500

* Correct analyses were obtained for all the new compounds described in this paper.

(a) This compound seems to be a mixture of 2-chloro-cis-5, trans-9-cyclododecadienone oxime and 2-chloro-trans-5, cis-10-cyclododecadienone oxime.

(b) All melting points are uncorrected.

2-chloro-5-cyclooctenone oxime, α-chlorocyclododecanone oxime, α-chloroxime from cis, trans, trans-1, 5, 9-cyclododecatriene, and 2-chloro-trans-5, trans-9-cyclododecadienone oxime, and corresponding 5-aminocycloalka[C]isoxazoles were obtained in excellent yields, of which results are sumarized in Table I.

α-Chlorocyclooctanone oxime and 2-chloro-5-cyclooctenone oxime were easily obtained from cyclooctene and cycloocta-1, 5-diene, respectively, with nitrosylchloride under irradiation6) or in the presence of hydrochloric acid3). α-Chlorocyclododecanone oxime was prepared from cis-cyclododecene and nitrosylchloride in the presence of hydrochloric acid7). α-Chlorocyclododecadienone oximes were prepared from cis, trans, trans-1, 5, 9-cyclododecatriene and trans, trans, trans-1, 5, 9-cyclododecatriene with nitrocylchloride using hydrochloric acid7), 8)

Since α-chlorocycloalkanone oximes are easily obtained from cycloolefins as mentioned above, the whole process presents an excellent synthetic methods of 5-aminocycloalka[C]isoxazoles from cycloolefins.

The application to acyclic α-chloroxime from isobutylene failed to give the isoxazole compound and afforded only a cyano-compound which resisted ring closure.

The reaction of acyclic olefins with nitrosyl chloride produced very unstable nitroso-compound which was hardly transformed into α-chloroxime, hence this method is not appicable to acyclic olefins.

Degradative work and related investigation of 5-aminocycloalca[C] isoxazoles will be published elsewhere.

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