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Reactions of 2-Chlorocycloalkanone Oximes. II.[1] Syntheses of 3-Aminocycloalka[C]isoxazoles[2]

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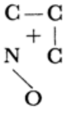
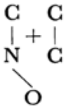
The displacement reactions of α-chlorocycloalkanone oximes with sodium cyanide in dimethyl sulfoxide or ethanol have been studied. It has been shown that 3-aminocycloalka[C]-isoxazoles can be obtained in excellent yields. α-Chlorooximes of cyclohexanone, cyclooctanone, cyclooocten-5-one, cyclododecanone, and cyclododecadien-5, 9-one have been subjected to the reaction, affording the corresponding isoxazole derivatives in 48, 96, 89, 95, and 90% yields respectively. The application of the method to 3-chloronorcamphor oxime and α-chlorooximes from acyclic olefins afforded cyanooximes; it failed to give isoxazole derivatives. The hydrogenation of 3-aminocycloocta[C]isoxazole gave 2-amino-1-cyclooctanecarbonamide by the hydrogenolysis of the nitrogen-oxygen bond of the isoxazole ring system. The amino-carbonamide was treated with either the base or acid to give 2-oxycyclooctanecarboxylic acid.

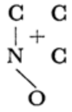
Various methods of synthesizing isoxazole derivatives have been extensively investigated, and excellent reviews have been published by Quilico[3] and by Kochetkov and Sokolov.[4] The known synthetic plans of an isoxazole ring can be expressed by the following three general schemes, indicated by I, II, and III:



I

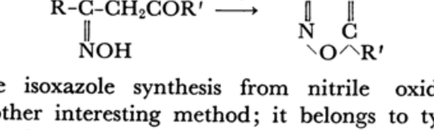


II



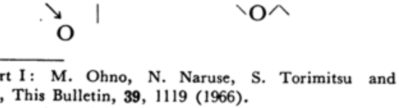
III

The reaction of 1, 3-dicarbonyl compounds with hydroxylamine is the method which has been used most widely for the synthesis of isoxazoles; it belongs to type I (Eq. 1);



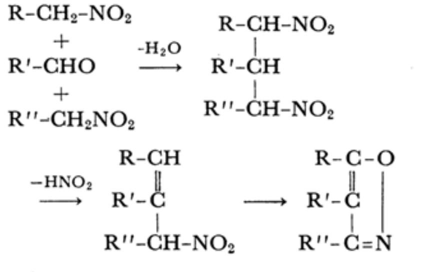
(1)

The isoxazole synthesis from nitrile oxides is another interesting method; it belongs to type II (Eq. 2):



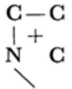
(2)

A special method for the formation of trisubstituted isoxazoles, one which starts from primary nitro derivatives, belongs to type III (Eq. 3):



(3)

During the investigation of the displacement reaction of 2-chlorocycloalkanone oximes with various nucleophilic reagents,[1] we have found a new method of synthesizing cycloalka[C]isoxazoles, one which is different from any of the methods mentioned above; it belongs to a new type, IV:



IV

In this report, the scope and limitations of the new synthesis and some reactions of 3-aminocycloalka[C]isoxazoles will be described.

2-Chlorocycloalkanone oximes were prepared readily by the reaction of cycloalkenes with nitrosyl chloride.[1] The reaction of 2-chlorocyclohexanone oxime with potassium or sodium cyanide in dimethyl sulfoxide or ethanol afforded a colorless crystalline material in a 48% yield. The infrared spectrum showed no absorption due to a nitrile group, but it did show absorptions at 3310 and 3160 cm^{-1} due to a primary amino group, and

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[1] Part I: M. Ohno, N. Naruse, S. Torimitsu and M. Okamoto, This Bulletin, **39**, 1119 (1966).

[2] Presented at the 17th Annual Meeting of the Chemical Society of Japan and for a preliminary communication, see M. Ohno and N. Naruse, *Tetrahedron Letters*, **1964**, 2151.

[3] A. Quilico, "The Chemistry of Heterocyclic Compounds," Vol. 17th, Interscience Pubishers, New York (1962), p. 1.

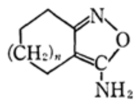
[4] N. K. Kochetkov and S. D. Sokolov, "Advances in Heterocyclic Chemistry," Vol. 2, Academic Press, New York (1963), p. 365.

TABLE I. YIELDS AND PHYSICAL PROPERTIES OF 3-AMINOCYCLOALKA[C]ISOXAZOLES

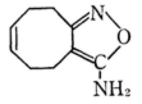
			3-Aminocycloalka[C]isoxazoles			
Cycloalkene	Formula	Yield, %	M. p., °C	UV, mμ	IR, cm^{-1}	
Cyclohexene	V	48	117—118	243 (ε, 7400)	3310 3160	1655 1640 1500
Cyclooctene	VI	96	77—78	252 (ε, 9700)	3380 3210	1650 1610 1500
Cyclooctadiene	VII	89	81.5—82.5	251 (ε, 8230)	3310 3180	1645 1610 1500
Cyclododecene	VIII	95	119—121	253 (ε, 7960)	3430 3280 3120	1650 1610 1495
cis, trans, trans-1, 5, 9-Cyclododecatriene	IX	95	148—150	244 (ε, 8000)	3420 3310 3180	1645 1615 1500
trans, trans, trans-1, 5, 9-Cyclododecatriene	X	90	131—134	256 (ε, 7900)	3420 3310 3180	1645 1915 1500

absorptions at 1655, 1640, and 1500 cm^{-1} due to a conjugated double bond system. The ultraviolet spectrum showed an absorption at 243 mμ (ε, 7400).

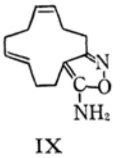
These spectral data, together with those of the elementary analysis, show that the structure of this compound can be identified as 3-amino-4, 5, 6, 7-tetrahydrocyclohexa[C]isoxazole (V). This has been confirmed further by a comparison of the melting point and spectra with those of an authentic sample.5)



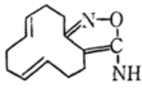
V $n=1$
VI $n=3$
VIII $n=7$



VII



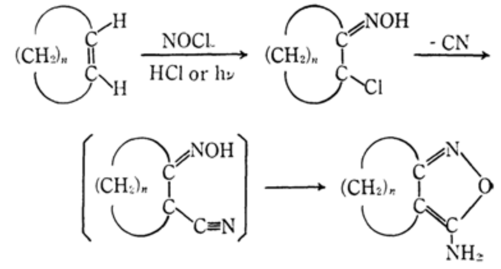
IX



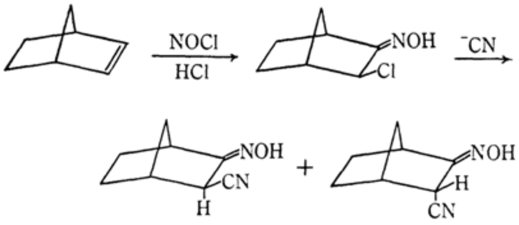
X

The formation of an isoxazole ring can be easily explained in terms of the displacement of an active chlorine atom with a cyanide anion, followed by an instantaneous ring closure between the oxime and the cyano groups.

This method has now been extended to α-chlorooximes of cyclooctanone, 5-cyclooctenone, and cyclododecanone, and to those1) from *cis, trans, trans*-1, 5, 9-cyclododecatriene, and *trans, trans, trans*-1, 5, 9-cyclododecatriene. The corresponding 3-aminocycloalka[C]isoxazoles, VI, VII, VIII, IX, and X, have been obtained in excellent yields. The results are summarized in Table I, and the synthetic method is expressed in the following successive formulae:



In order to clarify the scope and limitations of the reaction, the method was applied to norbornene, which is an example of the more strained olefins. The treatment of 3-chloronorcamphor oxime1) with sodium cyanide in dimethyl sulfoxide afforded a mixture of two stereoisomers (XI and XII) of 3-cyanonorcamphor oxime, which did not form isoxazole.



XI XII

This result suggests that the increase in ring strain is unfavorable for the formation of an isoxazole ring, but that the formation from 8- and 12-membered rings can be achieved easily because of no substantial ring strain. The application of this reaction to acyclic α-chlorooximes, which can be formed from isobutylene and butene-2,

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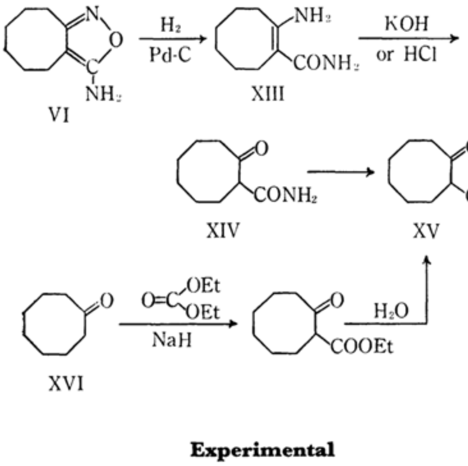
5) K. v. Auwers, Th. Bahr and E. Frese, *Ann.*, **441**, 68 (1925).

also failed to give the isoxazole compounds, but did give the corresponding cyano-compounds.

The hydrogenation of 3-aminocycloocta[C]-isoxazole and the chemical degradation of the hydrogenated product were investigated with a view to ascertaining some properties of the system. Just one-mole equivalent of hydrogen was absorbed by the catalytic hydrogenation of 3-aminocyclo-octa[C]isoxazole, using 5% palladium charcoal under atmospheric pressure; a crystalline product was thus obtained in a 98% yield. The infrared spectrum showed absorptions at 3400, 3300, and 3150 cm^{-1} due to a primary amino group, and absorptions at 1642 and 1610 cm^{-1} due to an amide group. The ultraviolet spectrum showed a maximum absorption at 242 mμ (ε, 8000), suggesting the presence of a conjugated amide. The spectral evidence is very consistent with 2-amino-1-cyclooctenecarbonamide (XIII). The hydrogenated product (XIII) was treated with either hydrochloric acid or potassium hydroxide to form 2-oxo-cyclooctylcarbonamide (XV). The prolonged treatment of the compound XIV with alkali gave 2-oxo-cyclooctylcarboxylic acid (XV), together with a small amount of cyclooctanone (XVI). The β-ketocarboxylic acid, XV, has been proved to be identical with an authentic sample prepared by the reaction of cyclooctanone with sodium hydride - ethyl carbonate and by subsequent hydrolysis. Therefore, the structure of the hydrogenated product (XIII) has been proved to be correct.



Experimental

3 - Amino - 4, 5, 6, 7-tetrahydrocyclohexa [C] isoxazole (V).—Freshly-prepared 2-chlorocyclohexanone oxime[1)] (10 g., 0.068 mol.) was treated with sodium cyanide (5 g., 0.10 mol.) in 50 ml. of ethanol under reflux for 2.5 hr. After the reaction, the sodium chloride formed and the unreacted sodium cyanide were removed by filtration and ether was added to the filtrate to remove the insoluble fraction. After the etherael solution had been evaporated, a brown solid was obtained. It was recrystallized from a mixed solvent of ether and petroleum ether to give a colorless crystalline material (4.5 g., 48%), m. p. 117—118°C. The infrared and ultraviolet spectra are shown in Table I.

Found: C, 61.19; H, 7.42; N, 20.23. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28%.

This substance was shown to be completely identical with an authentic sample[5,6)] by a mixed melting point determination and by a study of the spectral evidence. The authentic sample was prepared in the following way. Chlorocyan (7 g.) dissolved in 20 ml. of dioxane was added drop by drop to a solution of morpholine enamine (16 g.) of cyclohexanone in 130 ml. of dioxane at 0—5°C over a 2 hr. period. The reaction mixture was then allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and extracted with ether. After it had been dried and the ether had been evaporated, a yellow oil was obtained. It was distilled under reduced pressure to give a colorless oil, b. p. 120—130°C/1 mmHg, which was confirmed to be 2-cyanocyclohexanone. The cyanoketone was treated with hydroxylamine, generated from hydroxylamine hydrochloride and sodium carbonate, for 1 hr. After it had then been extracted with ether, the ethereal solution afforded colorless crystalline 3 - aminocyclohexa[C]isoxazole, m. p. 115—116°C, after recrystallization from ether - petroleum ether.

Found: C, 60.75; H, 7.30; N, 20.27. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28%.

3 - Amino - 4, 5, 6, 7, 8, 9 - hexahydrocycloocta[C]-isoxazole (VI).—2-Chlorocyclooctanone oxime (10 g., 0.056 mol.) dissolved in 30 ml. of dimethyl sulfoxide was vigorously stirred, over a 20 min. period, into a suspended solution of sodium cyanide (4 g., 0.081 mol.) in 40 ml. of dimethyl sulfoxide at 80—95°C. The reaction was continued for further 1.5 hr. at the same temperature. The reaction mixture was then treated with water and ether. The ethereal solution was dried and evaporated to give a pale yellow product (8.2 g., 96%). It was recrystallized from ether - petroleum ether to give a colorless analytical sample, m. p. 77—78°C.

Found: C, 65.26; H, 8.46; N, 16.70; O, 10.01. Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85; O, 9.63%.

The infrared and ultraviolet spectra are shown in Table I.

3 - Amino - 4, 5, 8, 9 - tetrahydrocycloocta [C] isoxazole (VII).—2-Chlorocyclooctenone oxime (2 g., 0.01 mol.) was treated with sodium cyanide (1 g., 0.02 mol.), in a manner similar to that described above, and a crystalline material, m. p. 81.5—82.5°C, was obtained in a 89% yield.

Found: C, 65.63; H, 7.41; N, 17.10. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06%.

3 - Amino - 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 - decahydrocyclododeca[C]isoxazole (VIII).—2-Chlorocyclododecanone oxime (3.0 g.) was treated with sodium cyanide (2 g.) in dimethyl sulfoxide in a manner similar to that described above; after the usual work-up, a crystalline product, m. p. 119—121°C, was obtained in a 95% yield.

Found: C, 70.14; H, 9.96; N, 12.56. Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60%.

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6) M. E. Kuehine, *J. Am. Chem. Soc.*, **81**, 5400 (1959).

3-Amino-4, 5, 8, 9, 12, 13-hexahydrododeca[C]-isoxazole (IX).—2-Chlorocyclododecadienone oxime (3.5 g., 0.015 mol.), prepared by the reaction of *cis, trans, trans*-1, 5, 9-cyclododecatriene with nitrosyl chloride, was treated with sodium cyanide (2 g., 0.04 mol.) suspended in dimethyl sulfoxide at 80—90°C for 3 hr. After the usual treatment of the reaction mixture, a pale-yellow solid (3.2 g., 95%) was obtained; it was recrystallized from ether-petroleum ether to give an analytical sample, m. p. 148—150°C.

Found: C, 71.32; H, 8.31; N, 12.83. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83%.

3-Amino-4, 5, 8, 9, 12, 13-hexahydro-*trans*-6, *trans*-10-cyclododeca[C]isoxazole (X).—2-Chlorocyclododecadienone oxime (5 g., 0.022 mol.), prepared by the reaction of *trans, trans, trans*-1, 5, 9-cyclododecatriene with nitrosyl chloride, was treated with sodium cyanide (3 g., 0.06 mol.) under the conditions described above. After usual treatment, a solid (4.2 g., 90%) was obtained; an analytical sample showed a m. p. of 131—134°C.

Found: C, 71.90; H, 8.31; N, 12.84. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83%.

The Reaction of 3-Chloronorcamphor Oxime with Sodium Cyanide.—3-Chloronorcamphor oxime (10 g.) was treated with two mole equivalents of sodium cyanide in dimethyl sulfoxide under the conditions described above. A solid product was obtained in a 90% yield, one showing a m. p. of 107—130°C after recrystallization from ether-petroleum ether. The infrared spectrum showed an absorption at 2245 cm^{-1} characteristic of a saturated nitrile group, besides those characteristic of the oxime group, and no absorption characteristic of an isoxazole ring system.

The NMR spectrum showed signals for the hydrogen next to the oxime group at τ 6.76 and τ 6.56, with coupling constants of 2.7 c. p. s. and 4.7 c. p. s. respectively. Therefore, the product must be a mixture of two stereoisomers (XI and XII) of 3-cyanonorcamphor oxime.

Found: C, 63.71; H, 6.71; N, 18.51. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65%.

The Hydrogenation of VI with Palladium Charcoal.—3-Aminocycloocta[C]isoxazole (VI, 1.0 g.) was hydrogenated in ethanol with 5% palladium charcoal (0.25 g.) under atmospheric pressure while being stirred. Hydrogen (131 ml.) was absorbed during a 3 hr. period; this is in accord with the calculated amount (129 ml. for one mole equivalent of hydrogen). After filtration the alcoholic solution was evaporated to dryness to give a colorless solid (1.0 g.). This was recrystallized from ethanol to give an analytical sample, m. p. 111—113°C.

Found: C, 64.01; H, 9.46; N, 16.16. Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.35%.

The infrared spectrum showed absorptions at 3400 (s), 3300 (w), 3150, 1642 (s), 1610 (s), and 1535 (m) cm^{-1}.

The ultraviolet spectrum showed a maximum at 242 mμ (ε, 8000). Therefore, the structure was identified as 2-amino-1-cyclooctene carbonamide (XIII).

The Hydrolysis of XIII with Potassium Hydroxide.—Compound XIII (3 g.) was added to a solution of potassium hydroxide (0.3 g.) dissolved in a mixture of water (25 ml.) and ethanol (25 ml.), the reaction mixture was then refluxed for 8 hr. After the ehanol had been evaporated, the residue was treated with hydrochloric acid and then extracted with ether-chloroform. The organic layer was dried and evaporated to dryness to give a pale-yellow solid (1.24 g., 42%). It was chromatographed on silica gel, using chloroform as an eluent; a crystalline substance, m. p. 106—108°C, was thus obtained. The infrared spectrum showed absorptions at 1710 cm^{-1} of carbonyl group, and 1670 and 1630 cm^{-1} of an amide group. The NMR spectrum showed signals at τ 6.48 for tertiary hydrogen. Therefore, the product was identified as 2-oxocyclooctanecarbonamide (XIV); it proved to be identical with an authentic sample prepared by the reaction of cyclooctanone and diethylcarbonate in the presence of sodium hydride and by subsequent hydrolysis.

Found: C, 64.07; H, 8.83; N, 8.34. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28%.

The prolonged treatment of XIII with potassium hydroxide afforded cyclooctanone as a by-product.

The Hydrolysis of XIII with Hydrochloric Acid.—Compound XIII (1.0 g.) was added to a mixture of ethanol (30 ml.) and 1 N hydrochloric acid (20 ml.); then the reaction mixture was refluxed for 2 hr. The oil obtained by the extraction with ether-methylene chloride was chromatographed on silica gel using chloroform. The solid (0.78 g., 80%) obtained was identical with that obtained from treatment with potassium hydroxide.