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Reactions of 2-Chlorocycloalkanone Oximes. III.[1] Displacement Reactions with Various Nucleophilic Reagents[2]

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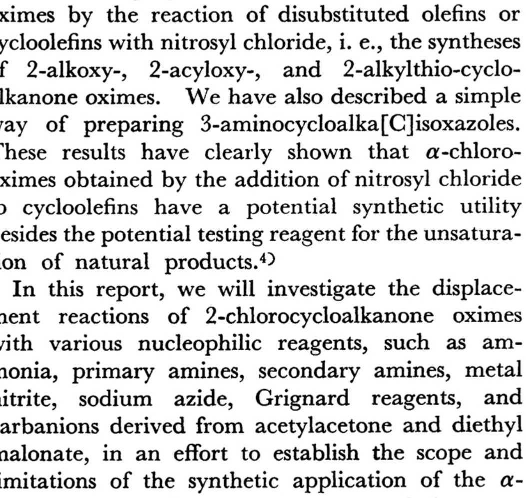
The displacement reactions of 2-chlorocycloalkanone oximes with various nucleophilic reagents, such as ammonia, primary and secondary amines, silver and sodium nitrite, sodium azide, Grignard reagents, and carbanions derived from acetylacetone and ethyl malonate, have been investigated. α-Alkylamino, α-nitro, α-azido, and α-alkyloximes of the 8- and 12-membered rings have been prepared in excellent yields, and those of the 6-membered ring, in moderate yields. It has been shown that 2-chlorocyclohexanone oxime hydrochloride can be treated directly with a large excess of the nucleophilic reagents. 2-Chlorocyclooctanone oxime was used in the free state, and 2-chloro-5, 9-cyclododecadienone oxime was first treated with nucleophilic reagents; the resulting α-substituted oximes of the 12-membered ring were hydrogenated to the corresponding saturated oximes with palladium charcoal. These reactions have shown that α-chlorocycloalkanone oximes have a potential synthetic utility.

In previous papers[1,3] of this series, we have described the preparation of 2-chlorocycloalkanone oximes by the reaction of disubstituted olefins or cycloolefins with nitrosyl chloride, i. e., the syntheses of 2-alkoxy-, 2-acyloxy-, and 2-alkylthio-cycloalkanone oximes. We have also described a simple way of preparing 3-aminocycloalka[C]isoxazoles. These results have clearly shown that α-chloro-oximes obtained by the addition of nitrosyl chloride to cycloolefins have a potential synthetic utility besides the potential testing reagent for the unsaturation of natural products.[4]

In this report, we will investigate the displacement reactions of 2-chlorocycloalkanone oximes with various nucleophilic reagents, such as ammonia, primary amines, secondary amines, metal nitrite, sodium azide, Grignard reagents, and carbanions derived from acetylacetone and diethyl malonate, in an effort to establish the scope and limitations of the synthetic application of the α-chlorooximes. The general scheme of the reactions is shown by the following equations:



As usual in our procedure, the displacement reactions of 2-chlorocyclooctanone oxime with various amines were first investigated in detail, since this starting material is the most stable to handle and can be prepared easily in a state of free oxime.[3]

The treatment of 2-chlorocyclooctanone oxime with ammonia did not form 2-aminocyclooctanone oxime, but it did give 2, 2'-iminodicyclooctanone oxime in a 30% yield. Reactions with morpholine, piperidine, *n*-butylamine, and hydrazine gave the corresponding α-aminooximes in excellent yields, as had been expected. The same reaction was then applied successfully to 2-chlorocyclohexanone oxime and 2-chlorocyclododecadienone oxime to give the corresponding α-aminooximes. 2-Aminocyclododecadienone oximes obtained were selectively hydrogenated to 2-aminocyclododecanone oximes by catalytic reduction with palladium charcoal.

Since cyclododecene is not easily available[3] and since only *trans*-cyclododecene reacts with nitrosyl chloride, 2-aminocyclododecanone oxime has been prepared conveniently by the reaction of *cis, trans, trans*-1, 5, 9-cyclododecatriene with nitrosyl chloride. In the case of 2-chlorocyclohexanone oxime, the hydrochloride[3] was treated directly with a large excess of amines. Since the hydrochloride is unstable and is considered to be a mixture of mono- and dihydrochloride,[5] the yields could not be estimated exactly.

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[1] Part II: M. Ohno and N. Naruse, This Bulletin, **39**, 1125 (1966).

[2] Presented at the 18th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1965.

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

[4] L. J. Beckham, W. A. Fessler and M. A. Kise, *Chem. Revs.*, **48**, 369 (1951).

[5] H. Saito, K. Nukada and M. Ohno, *Tetrahedron Letters*, **1964**, 2124.

VABLE I. DISPLACEMENT REACTIONS WITH VARIOUS AMINES

α-Chlorooxime	Reagent	Product	M, p., °C	Yield, %
2-Chlorocyclooctanone oxime	$NH_3/NaNH_2$	2,2′-Iminodicyclooctanone oxime (I)	182	30
2-Chlorocyclooctanone oxime	Morpholine	2-Morpholinocyclooctanone oxime (II)	133—134	86
2-Chlorocyclooctanone oxime	Pyrrolidine	2-Pyrrolidinocyclooctanone oxime (III)	161—162	93
2-Chlorocyclooctanone oxime	Piperidine	2-Piperidinocyclooctanone oxime (IV)	162—163	81
2-Chlorocyclooctanone oxime	Aniline	2-Anilinocyclooctanone oxime (V)	135—136	91
2-Chlorocyclooctanone oxime	*n*-Butylamine	2-(*n*-Butylamino)-cyclooctanone oxime (VI)	134—135	87
2-Chlorocyclooctanone oxime	Hydroxylamine	2-(Oxyamino)cyclooctanone oxime (VII)	144—145	80
2-Chloro-5,9-cyclododecadienone oxime	Morpholine	2-Morpholino-5,9-cyclododecadienone oxime (VIII)	108—110	71
2-Chloro-5,9-cyclododecadienone oxime	Pyrrolidine	2-Pyrrolidino-5,9-cyclododecadienone oxime (IX)	112—114	81
2-Chloro-5,9-cyclododecadienone oxime	Piperidine	2-Piperidino-5,9-cyclododecadienone oxime (X)	100—103	92
2-Chlorocyclohexanone oxime	Morpholine	2-Morpholino-cyclohexanone oxime (XI)	117—118	80—90
2-Chlorocyclohexanone oxime	Pyrrolidine	2-Pyrrolidinocyclohexanone oxime (XII)	120—121	80—90
2-Chlorocyclohexanone oxime	Piperidine	2-Piperidinocyclohexanone oxime (XIII)	117—118	75—85
2-Chlorocyclohexanone oxime	*n*-Butylamine	2-(*n*-Butylamino)-cyclohexanone oxime (XIV)	79— 80	72—80

TABLE II. DISPLACEMENT REACTIONS WITH NITRITE, AZIDE, GRIGNARD REAGENTS, AND CARBANIONS

α-Chlorooxime	Reagent(solv.)	Product	M. p., °C	Yield, %
2-Chlorocyclooctanone oxime	$AgNO_2$(ether)	2-Nitrocyclooctanone oxime (XV)	95— 96	89
2-Chlorocyclooctanone oxime	$NaNO_2$(DMSO)	2-Nitrocyclooctanone oxime (XV)	95— 96	66
2-Chlorocyclooctanone oxime	$NaN_3(CH_3CN)$	2-Azidocyclooctanone oxime (XVI)	52— 53	75
2-Chlorocyclooctanone oxime	$H_2C(COOEt)_2$	Ethyl-2-oximmocyclooctylmolonate (XXI)	89— 90	95
2-Chlorocyclooctanone oxime	$H_2C(COCH_3)_2$	2-(Diacetylmethyl)cyclooctanone oxime (XXIV)	155—156	72
2-Chloro-5,9-cyclododecadienone oxime	$AgNO_2$(OMSO)	2-Nitro-5,9-cyclododecadienone oxime (XVI)	115—117	80
2-Chloro-5,9-cyclododecadienone oxime	NaN_3(OHSO)	2-Azido-5,9-cyclododecadienone oxime (XVII)	63— 65	80
2-Chloro-5,9-cyclododecadienone oxime	PhMgBr	2-Phenyl-5,9-cyclododecadienone oxime (XIX)	133—135	52
2-Chloro-5,9-cyclododecadienone oxime	PhC≡CMgBr	2-(Phenylethynyl)-5,9-cyclododecadienone oxime (XX)	120—121	60
2-Chloro-5,9-cyclododecadienone oxime	$H_2C(COOEt)_2$	Ethyl-2-oximinocyclododecadienylmalonate (XXII)	91— 92	96
2-Chloro-5,9-cyclododecadienone oxime	$H_2C(COCH_3)_2$	2-(Diacetylmethyl)cyclododecadienone oxime (XXV)	159—160	98
2-Chlorocyclohexanone oxime	$H_2C(COOEt)_2$	Ethyl-2-oximinocyclohexylmalonate (XXIII)	71— 72	69
2-Chlorocyclohexanone oxime	$H_2C(COCH_3)_2$	2-(Diacetylmethyl)cyclohexanone oxime (XXVI)	154—155	13

As in the case of displacement reactions with sodium salts of alcohols, carboxylic acids and ethanethiol, maximum yields in the present investigation were also obtained when amounts greater than two mole equivalents of amines were used.[6] These results are shown in Table I.

In order to introduce a strong electron-withdrawing substituent to the α-position of the oxime group, 2-chlorocycloalkanone oximes were treated with silver and sodium nitrite. α-Chlorooximes of 8- and 12-membered rings gave the corresponding α-nitrooximes in excellent yields when treated with silver nitrite in dimethylsulfoxide. Since the same reaction with 2-chlorocyclooctanone oxime in ether did not form 2-nitrocyclooctanone oxime at all and since the starting material was then recovered, dimethylsulfoxide is the most effective solvent for this reaction in these cases. This method is thus a new way of preparing α-nitrocycloalkanone oximes, which were formerly prepared by the reaction of cycloolefins with nitric oxide in the presence of oxygen.[7]

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[6] A. Cornow and H. D. Jordan, *Chem. Ber.*, **94**, 1960 (1961).

[7] D. Klamann and W. Koser, *Angew. Chem.*, **76**, 591 (1964).

These results are summarized in Table II.

Next, the displacement reaction with azide ion has been investigated, since the negative charge of the ion is distributed over more than one polarizable atom and the ion is well known as a strong nucleophilic reagent.[8] The treatment of 2-chlorocyclooctanone oxime and of 2-chloro-5, 9-cyclododecadienone oxime with sodium azide in dimethylsulfoxide, ethanol or acetonitrile gave the corresponding α-azidooxime in 75 and 80% yields respectively. The structure is supported by the fact that the infrared spectrum showed a characteristic strong absorption, at 2140 cm^{-1}, of an asymmetric stretching vibration of azide.[9] Both of the α-azidooximes were hydrogenated with palladium charcoal in the presence of moist hydrochloric acid to give hydrochlorides of the corresponding α-aminoketones.

The reactions of α-chlorooximes of the acyclic system with Grignard reagents and carbanions to give higher oximes have been investigated by Dornow.[10] In the case of α-chlorooximes of cyclic systems, however, no investigation has been reported. To check this point, 2-chlorocycloalkanone oximes were treated with various Grignard reagents, such as phenylmagnesium bromide, ethylmagnesium bromide, and phenylethynylmagnesium bromide. The products from the reaction of the oximes of 2-chlorocyclohexanone and 2-chlorocyclooctanone with Grignard reagents were unstable oily materials, and all attempts to isolate pure substances were unsuccessful. However, the reaction of 2-chloro-5, 9-cyclododecadienone oxime with phenylmagnesium bromide and with phenylethynylmagnesium bromide gave the corresponding α-substituted oximes (Table II) successfully. It is of interest to note that 2-(phenylethyl)cyclododecadienone oxime has been converted into an allene derivative with sodium ethoxide.

Finally, displacement reactions with carbanions derived from various active hydrogen compounds were investigated. The treatments of the oximes of 2-chlorocyclohexanone, 2-chlorocyclooctanone, and 2-chloro-5, 9-cyclododecadienone with sodium salts of ethyl malonate and acetylacetone gave the corresponding α-substituted oximes (Table II). The yields of the products of the 8- and 12-membered rings were excellent, but those of the 6-membered ring were rather poor. The reactions of α-chlorocycloalkanone oximes with nitromethane, acetone, and ethyl acetate in the presence of a base did not afford the corresponding α-substituted oximes at all, but rather resinous matters, which might be formed by the polymerization of an α, β-unsaturated nitroso compound.

The accumulated evidence of the displacement reactions of 2-chlorocycloalkanone oximes described above have established the following points: (1) Most of the nucleophilic reagents replace the chlorine atoms of 2-chlorocyclolakanone oximes smoothly. (2) No appreciable amounts of unsaturated compounds were formed in the displacement reactions of α-chlorooximes of cycloolefins. (3) α-Chlorooximes of the 8- and 12-membered rings can be transformed into α-substituted oximes in excellent yields, but that of the 6-membered ring affords the product in a moderate yield. These results suggest that the stability of the α, β-unsaturated nitroso compounds formed as intermediates during the reactions is dependent upon the ring size. (4) The α-chlorooximes obtained by the addition of nitrosyl chloride to cycloolefins have a potential synthetic utility.

Experimental[11]

The Reaction of 2-Chlorocyclooctanone Oxime with Ammonia.—2-Chlorocyclooctanone oxime was treated with ammonia in the presence of sodium amide in tetrahydrofuran. A colorless solid was obtained in a 30% yield, m. p. 182—183°C. The infrared spectrum showed an absorption at 1650 cm^{-1} due to an oxime group.

Found: C, 64.81; H, 9.87; N, 14.06. M. W. 298. Calcd. for $C_{16}H_{29}N_3O_2$: C, 65.05; H, 9.90; N, 14.23%. M. W., 295.42.

2-Morpholinocyclooctanone Oxime (II).—Morpholine (19 g.) and ethanol (10 ml.) were placed in a 300-ml. three-necked round bottom flask equipped with a stirrer, a reflux condenser, and a dropping funnel. 2-Chlorocyclooctanone oxime (17.5 g.) dissolved in 70 ml. of ethanol was then added to the solution over a 30-min. period. The reaction mixture was then stirred at room temperature for 3 hr. After the solvent had been removed under reduced pressure, a solid product (19.7 g.) was obtained after washing the residue with water. It was recrystallized from ethanol to give an analytical sample, m. p. 133—134°C.

Found: C, 63.50; H, 9.73; N, 12.32. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80; N, 12.39%. IR: 3300—3000, 1640, 1500, 1115 cm^{-1} (KBr).

2-Pyrrolidinocyclooctanone Oxime (III).—2-Chlorocyclooctanone oxime (17.5 g.) dissolved in 70 ml. of ethanol was treated with pyrolidine (20 g.) in ethanol (100 ml.) for 3 hr. After the solvent had been removed and the residue washed with water, a solid product (17.5 g.) was obtained; this was recrystallized from ethanol to give an analytical sample, m. p. 161—162°C.

Found: C, 68.26; H, 10.46; N, 13.15. Calcd. for $C_{12}H_{22}ON_2$: C, 68.53; H, 10.54; N, 13.32%. IR: 3300—3000, 1650, 1512, 1120, 1095 cm^{-1} (KBr).

2-Piperidinocyclooctanone Oxime (IV).—2-Chlorocyclooctanone oxime (26.3 g.) was treated with piperidine (25 g.) in ethanol. After a work-up similar to that described above, a solid product (28.5 g.) was obtained; it was recrystallized from ethanol to give analytical sample, m. p. 162—163°C.

Found: C, 69.48; H, 10.76; N, 12.51. Calcd. for

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[8] E. S. Gould, "Mechanism and Structure in Organic Ohemistry," Henry Holt and Company, New York (1959), p. 250.

[9] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York (1958), p. 273.

[10] A. Donow and H. D. Jordan, *Chem. Ber.*, **94**, 76 (1961).

[11] All melting points are uncorrected.

$C_{13}H_{24}ON_2$: C, 69.60; H, 10.78; N, 12.49%. IR: 3300—3000, 1643, 1500, 1100 cm^{-1} (KBr).

2-Anilinocyclooctanone Oxime (V).—2-Chlorocyclooctanone oxime (17.5 g.) was treated with aniline (37 g.) in ethanol and, after a similar work-up, a solid product (21.2 g.) was obtained; it was then recrystallized from ethanol to give an analytical sample, m. p. 135—136°C.

Found: C, 72.27; H, 8.73; N, 11.86. Calcd. for $C_{14}H_{20}ON_2$: C, 72.38; H, 8.68; N, 12.06%. IR: 3370, 3200—3100, 1610, 1520, 1500, 750 cm^{-1} (KBr).

2-(*n*-Butylamino)cyclooctanone Oxime (VI).—2-Chlorocyclooctanone oxime (17.5 g.) was treated wtih *n*-butylamine (30 g.) in ethanol; after the usual work-up, a solid product (19 g.), m. p. 134—135°C, was obtained.

Found: C, 67.82; H, 11.34; N, 13.27. Calcd. for $C_{12}H_{24}ON_2$: C, 67.88; H, 11.39; N, 13.19%. IR: 3250, 1642, 1500, 1100 cm^{-1} (KBr).

2-(Oxyamino)cyclooctanone Oxime (VII).—In a 500-ml. three necked round bottom flask equipped with a stirrer, a dropping funnel, and a reflux condenser there were placed 200 ml. of ethanol containing hydroxylamine (about 7 g.) and water containing sodium carbonate (10 g.). 2-Chlorocyclooctanone oxime (17.5 g.) dissolved in 70 ml. of ethanol was stirred into the solution over a period of 30 min. The reaction mixture was then refluxed for 2 hr. After the usual work-up, as described in the case of 2-morpholinocyclooctanone oxime (II), a solid product (13.1 g.), m. p. 144—145°C, was obtained

Found: C, 55.64; H, 9.18; N, 16.11. Calcd. for $C_8H_{16}O_2N_2$: C, 55.79; H, 9.36; N, 16.27%. IR: 3250, 1645, 1510, 1110 cm^{-1} (KBr).

2 - Morpholino-5, 9-cyclododecadienone Oxime (VIII).—2-Chlorocyclododecadienone oxime (23 g.) was treated with morpholine (18 g.) in ethanol for 3 hr. After the solvent had been removed under reduced pressure, an oily product was obtained. By adding an excess of water to the product, a solid material (19.7 g.) was obtained and recrystallized from methanol to give an analytical sample, m. p. 106—109°C. The infrared spectrum showed absorptions at 1650, 980, and 707 cm^{-1} characteristic of an oxime group, and of *traus* and *cis* double bonds respectively, and absorptions at 1000—1100 cm^{-1} characteristic of an morpholino group.

Found: C, 68.81; H, 9.36; N, 10.09. Calcd. for $C_{16}H_{26}O_2N_2$: C, 69.03; H, 9.41; N, 10.06%.

The Hydrogenation of VIII.—2-Morpholinocyclododecadienone oxime (VIII, 2.8 g.) dissolved in 100 ml. of acetic acid was hydrogenated with 10% palladium charcoal (1 g.) under atmospheric pressure and at room temperature. Two mole equivalents of hydrogen was absorbed in 3 hr. After the solvent had been removed, the reaction product was treated with a 4 N sodium hydroxide solution to afford a colorless solid. This was recrystallized from methanol to give an analytical sample, m. p. 104—106°C. The infrared spectrum showed no absorption for carbon-carbon double bonds, and it was consistent with 2-morpholinocyclododecanone oxime.

Found: C, 67.89; H, 10.63; N, 9.90. Calcd. for $C_{16}H_{30}O_2N_2$: C, 68.04; H, 10.71; N, 9.92%.

2 - Pyrrolidino-5, 9-cyclododecadienone Oxime (IX).—2-Chlorocyclododecadienone oxime (23 g.) was treated with pyrrolidine (28 g.) in ethanol at 60—70°C for 2 hr. After the usual work-up, a solid product (21 g.) was obtained and recrystallized from methanol, m. p. 112—113°C.

Found: C, 73.13; H, 9.89; N, 10.61. Calcd. for $C_{16}H_{26}ON_2$: C, 73.24; H, 9.99; N, 10.68%. IR 3200, 1660, 1510, 970, 720 cm^{-1} (KBr).

This product (2.6 g.) was then hydrogenated in acetic acid (100 ml.) with 10% palladium charcoal (1 g.). After the absorption of two mole equivalents of hydrogen, the solvent was removed under reduced pressure; the residue was neutralized with a 4 N sodium hydroxide solution to afford a colorless solid in a nearly quantitative yield. It melted at 146—148°C after recrystallization from methanol. The infrared spectrum was consistent with the structure of 2-pyrrolidinocyclododecanone oxime.

Found: C, 72.18; H, 11.35; N, 10.53. Calcd. for $C_{16}H_{30}ON_2$: C, 72.13; H, 11.35; N, 10.52%. IR: 3200, 1650, 1510 cm^{-1} (KBr).

2-Piperidino-5, 9-cyclododecadienone Oxime (X).—2-Chlorocyclododecadineone oxime (24 g.) was treated with piperidine (35 g.) in ethanol at 60—70°C for 3 hr. After the usual work-up, a solid product (22.3 g.) was obtained and recrystallized from methanol to give an analytical sample, m. p. 100—103°C.

Found: C, 73.80; H, 10.20; N, 10.06. Calcd. for $C_{17}H_{28}ON_2$: C, 73.86; H, 10.21; N, 10.14%. IR: 3300, 1660, 1120, 960, 705 cm^{-1} (KBr).

A part of the product (2.8 g.) was hydrogenated in acetic acid (100 ml.) with 10% palladium charcoal (1 g.). Two mole equivalents of hydrogen were absorbed during a 3-hr. period. After a work-up similar to that described in the case of 2-morpholinocyclododecanone oxime, a solid product was obtained in a nearly quantitative yield; this was recrystallized from methanol to give an analytical sample, m. p. 96—97°C.

Found: C, 72.58; H, 11.45; N, 9.95. Calcd. for $C_{17}H_{32}ON_2$: C, 72.80; H, 11.50; N, 9.99%. IR: 3300—3000, 1640, 1110 cm^{-1} (KBr).

2-Morpholinocyclohexanone Oxime (XI).—Hydrochloride of 2-chlorocyclohexanone oxime (25 g.) dissolved in ethanol (100 ml.) was stirred, over a 30-min. period, into a solution of morpholine (50 g.) in ethanol (15 ml.) at 40°C; the reaction was then continued at 70°C for another hour. After the solvent had been removed, the residue solidified and was washed with water. When recrystallized from ether, it showed a m. p. of 117—118°C.

Found: C, 60.39; H, 9.06; N, 14.07. Calcd. for $C_{10}H_{18}O_2N_2$: C, 60.58; H, 9.15; N, 14.13%.

2-Pyrrolidinocyclohexanone Oxime (XII).—The hydrochloride of 2-chlorocyclohexanone oxime (12 g.) was treated with pyrrolidine (23 g.) in ethanol. After the usual work-up, described above, a solid product (10.7 g.) was obtained and recrystallized from ether, m. p. 120—121°C.

Found: C, 65.78; H, 9.92; N, 15.35. Calcd. for $C_{10}H_{18}ON_2$: C, 65.89; H, 9.96; N, 15.37%.

2-Piperidinocyclohexanone Oxime (XIII).—The hydrochloride of 2-chlorocyclohexanone oxime (9.5 g.) was treated with piperidine (25 g.) in ethanol. After the usual work-up, a solid product (8.5 g.) was obtained and recrystallized from ether, m. p. 117—118°C.

Found: C, 67.24; H, 10.23; N, 14.26. Calcd. for $C_{11}H_{20}ON_2$: C, 67.30; H, 10.27; N, 14.27%.

2-(*n*-Butylamino)cyclohexanone Oxime (XIV).—The hydrochloride of 2-chlorocyclohexanone oxime (18.4 g.) was treated with *n*-butylamine (36 g.) in ethanol.

After the usual work-up, a solid product (16 g.) was obtained and recrystallized from ether, m. p. 79—80°C.

Found: C, 65.39; H, 10.88; N, 15.15. Calcd. for $C_{10}H_{20}ON_2$: C, 65.17; H, 10.94; N, 15.20%.

2-Nitrocyclooctanone Oxime (XV).—Silver nitrite (13.2 g.) and ether (100 ml.) were placed in a 500-ml. three-necked round-bottom flask equipped with a stirrer, a condenser, and a dropping funnel. A solution of 2-chlorocyclooctanone oxime (15 g.) dissolved in 150 ml. of ether was then vigorously stirred into the above suspended solution over a 1-hr. period, after which the reaction was continued for 4 hr. at room temperature. The precipitate of silver chloride was removed by filtration, and the filtrate was washed with water. The ethereal solution was dried over sodium sulfate and evaporated to dryness to give a yellow solid (14.2 g., 89.3%). It was dissolved in hot ligroin and treated with activated carbon to give a pale-yellow solid, which was then further recrystallized from ligroin to afford colorless needles, m. p. 95—96°C. The infrared spectrum showed absorptions at 3310 and 1640 cm^{-1} for the oximino group, and at 1550 cm^{-1} (strong) for the nitro group.

Found: C, 51.71; H, 7.66; N, 14.85. Calcd. for $C_8H_{14}O_3N_2$: C, 51.60; H, 7.58; N, 15.04%.

In a separate run, 2-chlorocyclooctanone oxime (5 g.) was treated with silver nitrite (4.5 g.) in dimethylsulfoxide at room temperature for 1 hr. The ether extract of the reaction mixture was dried and evaporated to dryness to give 4.5 g. of a yellow solid, which was confirmed to be identical with the product obtained from the above reaction using ether as the solvent. When sodium nitrite was used in dimethylsulfoxide, 2-nitrocyclooctanone oxime was obtained in about a 66% yield, but in ether no detectable amount of 2-nitrocyclooctanone oxime was obtained.

2-Nitro-5, 9-cyclododecadienone Oxime (XVI).—2-Chlorocyclododecadienone oxime (10 g.) was treated with silver nitrite (7 g.) in dimethylsulfoxide at room temperature for 1 hr. After treatment similar to that described above, a yellow solid (8.4 g.) was obtained; it was recrystallized from ligroin to give a colorless solid, m. p. 115—117°C. The infrared spectrum showed absorptions at 980 and 707 cm^{-1} characteristic of *trans* and *cis* double bonds respectively, at 3320 and 1640 cm^{-1} characteristic of an oximino group, and at 1560 cm^{-1} characteristic of nitro group.

Found: C, 60.54; H, 7.68; N, 11.47. Calcd. for $C_{12}H_{18}O_3N_2$: C, 60.48; H, 7.61; N, 11.76%.

2-Azidocyclooctanone Oxime (XVII).—2-Chlorocyclooctanone oxime (36 g.) was treated with sodium azide (14g.) in acetonitrile while being stirred and heated on a steam bath for 5 hr. To the reaction mixture, water (500 ml.) was added, and the ethereal extract was dried and evaporated to dryness to give a solid product. It was recrystallized from a mixed solvent of ether and petroleum ether to give an analytical sample, m. p. 52—53°C.

Found: C, 52.45 : H, 7.69; N, 30.66. Calcd. for $C_8H_{14}ON_4$: C, 52.73; H, 7.74; N, 30.65%.

The product was hydrogenated in moist ethanol containing hydrochloric acid with 5% palladium charcoal under atmospheric pressure. The infrared spectrum of the hydrogenated product, m. p. 186—188°C (decomp.) showed a strong absorption at 1705 cm^{-1} characteristic of 8-membered ring ketone and one at 3300 cm^{-1} characteristic of an amino group. Thus the structure may be though to be that of the hydrochloride of 2-aminocyclooctanone.

2-Azido-5, 9-cyclododecadienone Oxime (XVIII).—2-Chlorocyclododecadienone oxime (68.25 g.) was treated with sodium azide (23.4 g.) in dimethyl sulfoxide (600 ml.) while being vigorously stirred and heated on a steam bath for 12 hr. After treatment similar to that described above, a solid product (56 g.) was obtained and recrystallized from a mixed solvent of ether and petroleum ether to give a colorless material, m. p. 63—65°C.

Found: C, 61.77; H, 7.85; N, 24.11. Calcd. for $C_{12}H_{18}ON_4$: C, 61.51; H, 7.74; N, 23.91%.

In order to confirm the structure, the product was hydrogenated with 5% palladium charcoal in moist ethanol containing hydrochloric acid. The infrared spectrum of the hydrogenated procuct, m. p. 223°C (decomp.), showed a strong absorption at 1704 cm^{-1} characteristic of 12-membered ring ketone, and one at 3320 cm^{-1} characteristic of an amino group, with neither the absorption at 980 nor that at 707 cm^{-1} characteristic of *trans* and *cis* double bonds respectively.

Found: C, 61.30; H, 10.28; N, 6.06; Cl, 15.30. Calcd. for $C_{12}H_{24}NOCl$: C, 61.20; H, 10.35; N, 5.96; Cl, 15.05%.

2-Phenyl-5, 9-cyclododecadienone Oxime (XIX).—In a 2-l. three necked round-bottom flask equipped with a stirrer, a condenser, and a dropping funnel, magnesium (7.3 g.) was placed. A solution of bromobenzene (47.1 g.) dissolved in tetrahydrofuran (400 ml.) was then vigorously stirred into the reaction vessel. After phenyl magnesium bromide had been made, 2-chlorocyclododecadienone oxime (22.75 g.) dissolved in tetrahydrofuran (100 ml.) was added slowly at 20—25°C and the reaction was continued for 15 hr. at room temperature. The reaction mixture was treated with ice, diluted hydrochloric acid, and extracted with ether. The ethereal extract was treated with a sodium carbonate solution and then with a saturated solution of sodium chloride, dried, and evaporated to dryness to give a crude product (20 g.). This was recrystallized from methanol, m. p. 133—135°C.

Found: C, 80.13; H, 8.54; N, 5.12. Calcd. for $C_{18}H_{23}ON$: C, 80.25; H, 8.61; N, 5.20%. IR: 3300, 1660, 960, 760, 710 cm^{-1} (KBr).

2 - (Phenylethynyl)cyclododecadienone Oxime (XX).—2-Chlorocyclododecadienone oxime was treated with phenylethynyl magnesium bromide under conditions similar to those described above. 2-(Phenylethynyl)-5, 9-cyclododecadienone oxime was thus obtained in a 60% yield, m. p. 120—121°C.

Found: C, 81.63; H, 7.90; N, 4.67. M. W., 306. Calcd. for $C_{20}H_{23}ON$: C, 81.87; H, 7.90; N, 4.77%. M. W., 293.

The compound XX was treated with sodium ethoxide to afford an isomer, m. p. 136—139°C. The infrared spectrum showed an absorption at 1930 cm^{-1} characteristic of allene and not the absorption at 2240 cm^{-1} characteristic of the acetylene group observed in the compound XX.

Found: C, 81.92; N, 8.01; N, 4.77%.

Ethyl *α*-Oximinocyclooctylmalonate (XXI). — Sodium salt of ethyl malonate was prepared by a reaction of sodium (5.3 g.) with ethyl malonate (35 ml.) in ether (200 ml.). To the solution there was added, drop by drop, 2-chlorocyclooctanone oxime (17.5 g.)

dissolved in ether (100 ml.) over a 1-hr. period; the reaction was then continued for an additional 2 hr. The excess of the sodium salts was decomposed with ice water, and the reaction mixture was extracted with ether. The ethereal extract was dried and cooled at 0°C to deposit a colorless solid. After the solid had been separated by filtration, the filtrate was evaporated to remove the ether and the ethyl malonate, thus giving a solid product. The combined solid materials (28.5 g.) were recrystallized from ethanol to give a pure substance, m. p. 89—90°C. The infrared spectrum was consistent with that of ethyl α-oximinocyclooctylmalonate (XXI).

Found: C, 60.35; H, 8.37; N, 4.66. M. W., 300. Calcd. for $C_{15}H_{25}O_5N$: C, 60.18; H, 8.42; N, 4.68%. M. W., 299.

Ethyl α - Oximinocyclododecadienylmalonate (XXII).—According to a procedure similar to that described above, compound XXII (33.8 g.) was prepared by the reaction of 2-chlorocyclododecadienone oxime (22.8 g.) with sodium salt of ethyl malonate. It was recrystallized from ethanol to give an analytical sample, m. p. 91—92°C.

Found: C, 64.93; H, 8.32; N, 3.99. M. W., 359. Calcd. for $C_{19}H_{29}O_5N$: C, 64.95; H, 8.35; N, 3.94%. M. W., 351.

Ethyl α-Oximinocyclohexylmalonate (XXIII).—According to a procedure similar to that described above, compound XXIII (18.8 g.) was prepared by the reaction of hydrochloride of 2-chlorocyclohexanone oxime with sodium salt of ethylmalonate. It was recrystallized from ethanol to give an analytical sample, m. p. 71—72°C.

Found: C, 57.41; H, 7.78; N, 5.07. M. W., 274. Calcd. for $C_{13}H_{21}O_5N$: C, 57.55; H, 7.80; N, 5.16. M. W., 271.

2-(Diacetylmethyl)cyclooctanone Oxime (XXIV).—Sodium salt of acetylacetone was prepared from sodium (5.3 g.) and acetylacetone (50 ml.) in ether (200 ml.). 2-Chlorocyclooctanone oxime (17.5 g.) was then stirred into the above solution at 0—5°C over a 1-hr. period. After 2 hr., the reaction mixture was treated with ice water in ordor to decompose the excess of the sodium salt. A colorless solid (17.2 g.) was thus obtained; it was recrystallized from ethanol, m. p. 155—156°C. IR (cm^{-1}): 3010, 2925, 2850, 2560, 1708, 1605, 1255, 1205, 1160, 1150. UV: λ_{max}^{EtOH} 240 mμ (ε, 10700); NMR(τ), 6.30 (1 H, doublet), 6.77 (1 H, multiplet), 7.65 (6 H, singlet). This spectroscopic evidence shows that the structure is 2-(diacetylmethyl)cyclooctanone oxime (XXIV).

Found: C, 65.31; H, 8.85; N, 5.82. M. W., 249. Calcd. for $C_{13}H_{21}O_3N$: C, 65.24; H, 8.85; N, 5.85%. M. W., 239.

2 - (Diacetylmethyl)cyclododecadienone Oxime (XXV).—According to a procedure similar to that described above, compound XXV (29 g.) was obtained by the reaction of 2-chlorocyclododecadienone oxime (22.8 g.) with sodium salt of acetylacetone. It was recrystallized from ethanol to give an analytical sample, m. p. 159—160°C. IR (cm^{-1}): 3000—3100, 1705, 1595; UV: λ_{max}^{EtOH} 241 mμ (ε, 13000). NMR (τ), 4.5 (4H, m), 6.30 (1H, d), 6.9 (1H, m), 7.67 (6H, singlet).

Found: C, 69.90; H, 8.54; N, 4.68. M. W., 308. Calcd. for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65; N, 4.81%. M. W., 301.

2-(Diacetylmethyl)cyclohexanone Oxime (XXVI).—According to a procedure similar to that described above, compound XXVI (2.8 g.) was prepared by the reaction of hydrochloride of 2-chlorocyclohexanone oxime (18.4 g.) with sodium salt of acetylacetone. It was recrystallized from ethanol, m. p. 154—155°C. IR (cm^{-1}), 3050, 1710, 1630. UV: λ_{max}^{EtOH} 239.5 mμ (ε, 10000).

Found: C, 62.45; H, 8.19; N, 6.59. M. W., 210. Calcd. for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.63%. M. W., 211.