The Reactions of C(α), *O*-Dilithiooximes, C(α), *N*-Dilithiophenylhydrazones, and C(α), *N,N*-Trilithiohydrazones with Diethyl Oxalate to Give Biisoxazoles, Bipyrazoles, and Pyridazones.

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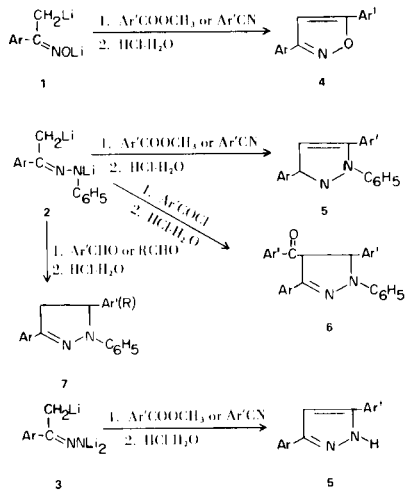
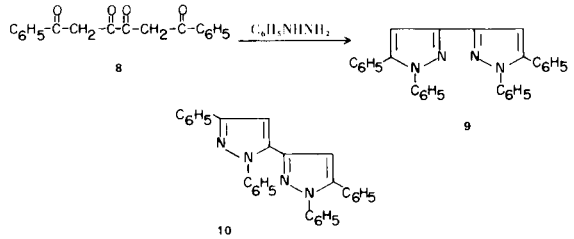
Several C(α), *O*-dilithiooximes were condensed with diethyl oxalate and acid-cyclized to give biisoxazoles. Only dilithio *p*-fluoroacetophenone phenylhydrazone gave the bipyrazole when condensed with this diester. Other C(α), *N*-dilithiophenylhydrazones and several C(α), *N,N*-trilithiohydrazones were condensed with diethyl oxalate and acid-cyclized to give the intramolecular 4-hydroxy-3-pyridazones. Several non-cyclized intermediates were isolated and a reaction mechanism is presented.

We have recently prepared numerous C(α), *O*-dilithiooximes **1**, C(α), *N*-dilithiophenylhydrazones **2**, and C(α), *N,N*-trilithiohydrazones **3**, and condensed these reactive intermediates with esters, nitriles, acid chlorides and aldehydes, followed by acid-cyclization to give isoxazoles **4**, pyrazoles **5**, 4-acylpyrazoles **6** and 2-pyrazolines **7** (4-9) (Scheme I).

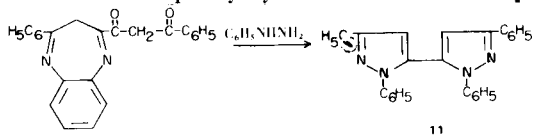
Scheme I



It was of additional interest to treat these multilithio reactants with bifunctional esters, such as diethyl oxalate, in order to prepare the more complex bipyrazoles and biisoxazoles. This method promised to have the advantage of rapid synthetic procedure using readily available starting materials, and appeared to be easier than synthetic methods already reported (10 and 11). For example, according to Finar (12) the reaction of two moles of phenylhydrazone with 1,6-diphenyl-1,3,4,6-tetraketohexane **8** gave a mixture of 1,1′,5,5′-tetraphenyl-3,3′-bipyrazole **9** and 1,1′,3′,5-tetraphenyl-3,5′-bipyrazole **10**.

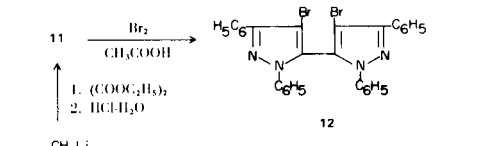


Finar also reported (13) the synthesis of a third possible isomer in this series, 1,1′,3,3′-tetraphenyl-5,5′-bipyrazole **11** by the reaction of phenylhydrazine with the diazepine of **8**.

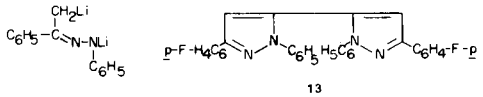


Acetophenone phenylhydrazone was converted to its dilithio derivative by treatment with two molar equivalents *n*-butyllithium, followed by the addition of 0.25 molar equivalents of diethyl oxalate, (1:2:0.25 - phenylhydrazone:base:diester - see Experimental). During a single

instance, the resulting mixture was acid-cyclized to give **11** in 55% yield. While this material had been reported (13) previously, its melting point (195-195.5°) did not favorably compare with the melting point (187.5-188°) of the material prepared during this investigation. In addition, the structure of **11** was supported by elemental analysis, infrared spectra containing characteristic pyrazole absorptions, high resolution mass spectra, and conversion to its known 4,4′-dibromo derivative **12**. While this single result was not



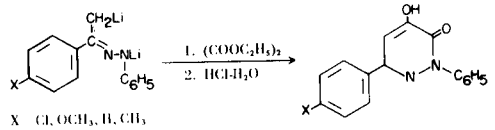
12



13

readily reproducible, the dilithiophenylhydrazone of *p*-fluoroacetophenone was condensed with diethyl oxalate and cyclized to 3,3′-di(*p*-fluorophenyl)-1,1′-diphenyl-5,5′-bipyrazole **13** in 34%, and this result was readily reproducible.

Interestingly, the C(α), *N*-dilithiophenylhydrazones of *p*-chloroacetophenone and *p*-methoxyacetophenone were condensed with diethyl oxalate to give, after acid cyclization, 4-hydroxy-3-pyridazones **14** and **15** in 71% and 52% yields, respectively. Some 4-hydroxy-3-pyridazones have

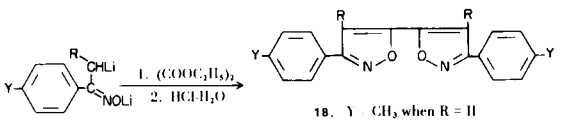


X = Cl, OCH_3, H, CH_3

14, X = Cl
15, X = OCH_3
16, X = H
17, X = CH_3

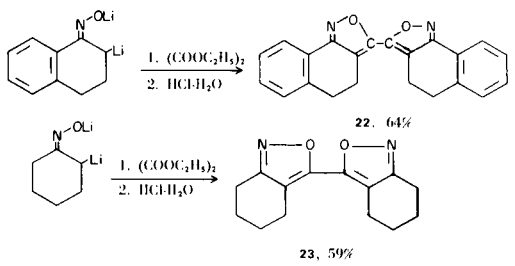
been prepared from halopyridazones, (14 and 15), and their properties indicate that they exist in the monoenol rather than diketo form. The preparation of 4-hydroxy-3-pyridazones from acetophenone and 4-methylacetophenone dianions resulted in a 72% and 89% yield of these materials **16** and **17** (16), respectively.

In an analogous manner, the C(α), *O*-dilithiooximes of acetophenone, cyclohexanone, 4-methylacetophenone, propiophenone, and α-tetralone were prepared and condensed with diethyl oxalate and acid-cyclized to give the expected biisoxazoles **18-23** in 22-77% yield (see Experimental).



Y = H, CH_3, and R = H
Y = H and R = CH_3

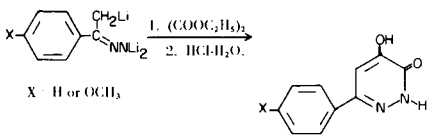
18, Y = CH_3 when R = H
19, Y = H when R = H
20, Y = H and R = CH_3
21, Y = OCH_3 and R = H



22, 64%

23, 59%

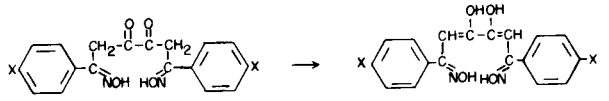
The C(α), *N*,*N*-trianions of acetophenone and *p*-methoxyacetophenone were also prepared and condensed with diethyl oxalate (hydrazone:base:ester 1:3:0.25), and the intermediates were acid cyclized to give the 4-hydroxypyridazones **24** and **25** in 24% and 22% yield, respectively.



X = H or OCH_3

24, X = H
25, X = OCH_3

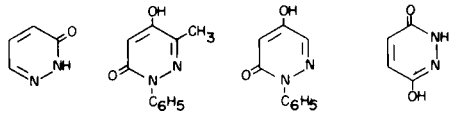
In several cases where the cyclization was incomplete, intermediates **26** and **27** were isolated in good yield and characterized.



26, X = OCH_3
27, X = F

The infrared and mass spectra of the pyridazones are worthy of further discussion. The infrared spectrum of 3-pyridazone **28** showed that it exists primarily in the lactam form in both the solid state and solution. Mason (17) recorded an C=O stretching absorption at 1681 cm^{-1} (5.95μ) for **28** in chloroform solution, while the solid state spectrum of this material taken by Sheinker and Pomerantsev (18) exhibited bands at 3380 cm^{-1} (2.96μ) and 1650 cm^{-1} (6.06μ) for the N-H and C=O stretching vibrations, respectively.

Hydroxypyridazones apparently exist predominently as enol-lactams as shown by the spectra of compound **29** (15), **30** (19), and **31** (20).

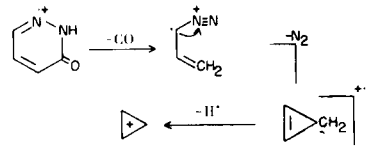


28 **29** **30** **31**

Compounds **14**, **15**, **16**, **17**, **24** and **25** exhibited broad O-H stretching bands in the 3.0-4.0μ region, which indicated strong hydrogen bonding in these derivatives, and the C=O stretching absorptions occurred at 5.96-6.06μ, which closely corresponded to values reported for 3-pyridazones

(17 and 18). The spectra of **24** and **25** also contained N-H stretching bands at 3.0μ (see Experimental for other ir data). Mass spectra data was obtained for pyridazones **14**, **15**, **24** and **25** (see Experimental). The fragmentation of 3-pyridazones reportedly (21) involved loss of CO followed by loss of N_2 and H· (Scheme II). The spectra of compounds **24** and **25** contained major ions at M-28, M-56, and M-57 consistent with the fragmentation mode M-CO-N_2-H· and in addition contained ions at M-85 indicating loss of a second CO fragment.

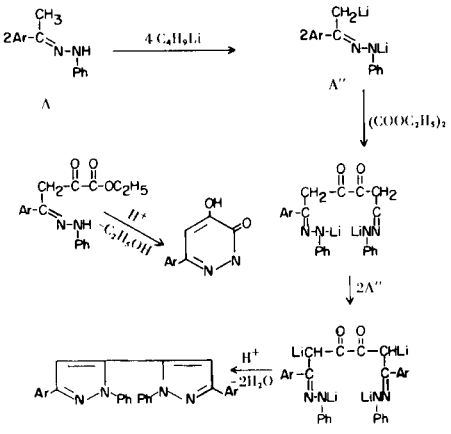
Scheme II



The *N*-substituted pyridazones **14** and **15** also appeared to undergo initial loss of CO as indicated by prominent M-28 ions, and the M-161 peaks observed in their spectra may arise through loss of a second CO fragment and the $C_6H_5N_2$ moiety.

The ratio of reactants (1 phenylhydrazone: 2 base: ¼ diester) was consistent with a modified Claisen condensation (22) as shown in Scheme III. The pyridazones were logically formed by cyclization of the monocondensation intermediates.

Scheme III



The syntheses described are a good method for the preparation of biisoxazoles and 4-hydroxy-3-pyridazones. They have the advantage of requiring readily available starting materials, a short experimental procedure, and the products are readily isolated and purified in fair to good yield.

EXPERIMENTAL

Analyses were performed by M-H-W Laboratories, Garden City, Michigan and Robertson Laboratory, Florham Park, New Jersey, Infrared spectra were obtained on Perkin-Elmer Model 137, 237, and 700 Spectrometers. The nmr spectra were obtained using a Varian A-60 nmr Spectrometer using trifluoroacetic acid as solvent, and shifts are reported in parts per million down-field from an internal tetramethyl silane (TMS) standard. Mass spectra were taken at Research Triangle Institute for Mass Spectrometry, Durham, N. C., on an MS-902 Mass Spectrometer. Melting points were taken in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately before use, or it was taken from a newly opened bottle (Matheson-Coleman Bell). The *n*-butyllithium was obtained as a 1.6 *M* hexane solution from Foote Mineral Co., Exton, Pennsylvania or Lithium Corporation of America, Bessemer City, N. C.

General Procedure for Conversion of a Hydrazone or Phenylhydrazone to its C(α)-Lithio Derivative.

To a stirred solution of 0.050 mole of phenylhydrazone in 100 ml. of THF, which was cooled to 0° under a nitrogen atmosphere, was added during 5 minutes, 62 ml. (0.10 mole) of 1.6 *M* *n*-butyllithium. After 30 minutes, the solution was assumed to contain 0.050 mole of dilithio derivative. Hydrazones were similarly treated with 93 ml. (0.150 mole) of 1.6 *M* *n*-butyllithium, and the solutions were assumed to contain 0.050 mole of trilithio derivative after 2½-3 hours. The lithio derivatives thus prepared were condensed with dithyl oxalate as described below.

General Procedure for the Condensation-Cyclization of C(α)-Lithio Derivatives with Diethyl Oxalate.

A 0.0125-mole sample of diethyl oxalate dissolved in 100 ml. of THF was added during 5-10 minutes to a solution containing 0.050 mole of C(α)-lithio derivative (prepared as described above). After stirring at 0° for ½-1 hour, the mixture was acidified with 100 ml. of 3 *N* hydrochloric acid. The mixture was then heated at reflux temperature for 1 hour and cooled, and the layers were separated. The aqueous layer was neutralized with sodium bicarbonate and extracted with ether. The THF layer and ether extracts were combined, dried with anhydrous magnesium sulfate, filtered and evaporated. The residue was recrystallized from an appropriate solvent as noted.

Bipyrazoles.

1,1′,3,3′-Tetraphenyl-5,5′-bipyrazole (**11**).

This compound was obtained by the above procedure from acetophenone phenylhydrazone (10.52 g., 0.050 mole) and diethyl oxalate (1.83 g., 0.0125 mole). Crystallization of the crude product from 50 ml. of 95% ethanol gave 3.02 g. (55%) of **11**, m.p. 183-186°. Recrystallization from methanol gave an analytical sample, m.p. 187.5-188°, lit (13), m.p. 195-195.5°; ir (potassium bromide): 7.27, 6.72, 7.40, (Ar-N), 10.45, 10.58 μ.

Anal. Calcd. for $C_{30}H_{22}N_4$: C, 82.17; H, 5.06; N, 12.78; m/e 438.1844. Found: C, 82.02; H, 5.07; N, 12.86; m/e 438.1843.

4,4′-Dibromo-1,1′,3,3′-tetraphenyl-5,5′-bipyrazole (**12**).

A 0.5 g. sample of **11** was dissolved in 100 ml. of glacial acetic acid with 5 ml. of bromine and the solution was heated on a hot plate for 3 hours. After cooling the solution was allowed to stand overnight and the crystals were filtered off. Recrystallization from acetic acid gave colorless crystals, m.p. 174-175°, lit (13) m.p. 175-175.5°.

3,3'-Di(*p*-fluorophenyl)-1,1'-diphenyl-5,5'-bipyrazole (**13**).

This compound was obtained by the above procedures from *p*-fluoroacetophenone phenylhydrazone (11.41 g., 0.050 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product was treated with refluxing 95% ethanol, cooled, and filtered to give 2.63 g. (44%) of **13**, m.p. 205-210°. Recrystallization of an analytical sample from 95% ethanol gave colorless crystals, m.p. 210-211°; ir (potassium bromide): 6.25, 6.72, 7.45 (Ar-N), 10.50, 10.62 μ.

Anal. Calcd. for $C_{30}H_{20}F_2N_4$: C, 75.94; H, 4.25; N, 11.81; m/e 474.1656. Found: C, 76.23; H, 4.34; N, 11.68; m/e 474.1664.

Pyridazones.

6-(*p*-Chlorophenyl)-4-hydroxy-2-phenyl-3-pyridazone (**14**).

This compound was obtained by the above procedures from *p*-chloroacetophenone phenylhydrazone (12.26 g., 0.050 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product was recrystallized from 95% ethanol to give 2.65 g. (71%) of **14**, m.p. 235-236°; ir (potassium bromide): 3.14 μ (OH) and 6.06 μ (C=O); mass spectrum: (70 eV) m/e (relative intensity), 300 (35), 299 (21), 298 (100, M^+), 297 (8), 272 (8), 270 (16, M-28), 139 (3), 137 (7, M-161), 105 (9), 91 (9), 81 (6), 77 (15), 69 (10), 57 (6), 55 (7), 44 (5), 43 (5), 41 (9), and 40 (17).

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38; m/e 298.0509. Found: C, 64.67; H, 3.60; N, 9.24; m/e 298.0507.

4-Hydroxy-6-(*p*-methoxyphenyl)-2-phenyl-3-pyridazone (**15**).

This compound was obtained by the above procedures from *p*-methoxyacetophenone phenylhydrazone (12.02 g., 0.050 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product was treated with 100 ml. of 95% ethanol under reflux, cooled, and filtered to give 1.90 g. (52%) of **15**, m.p. 196.5-198°. Recrystallization from 95% ethanol gave an analytical sample, m.p. 206-207.5°; nmr (TFA): δ 4.00 (3H, s, $-OCH_3$), 7.48 (1H, s, =CH-), 7.14 and 7.79 (4H, AB, J = 9 Hz); ir (potassium bromide): 3.15 μ (OH) and 6.05 μ (C=O); mass spectrum: (70 eV) m/e (relative intensity), 295 (23), 294 (100, M^+), 266 (18, M-28), 251 (6), 174 (12), 161 (7), 146 (11), 134 (6), 133 (40, M-161), 132 (7), 118 (5), 91 (9), 89 (8), 81 (7), 77 (12), 69 (9), 57 (9), 95 (10), 51 (5), 43 (9), and 41 (12).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.80; N, 9.52; m/e 294.1004. Found: C, 69.33; H, 4.63; N, 9.2; m/e 294.1001.

2,6-Diphenyl-4-hydroxy-3-pyridazone (**16**).

This compound was obtained by the above procedure from acetophenone phenylhydrazone (10.50 g., 0.05 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product was recrystallized from 95% ethanol to give 2.39 g. (72%) of **16**, m.p. 234-235.5°; ir (nujol): 3.18 μ (OH) and 6.08 μ (C=O).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.91; H, 4.77; N, 10.39.

4-Hydroxy-2-phenyl-6-*p*-tolyl-3-pyridazone (**17**).

This compound was obtained by the above procedure from 4-methylacetophenone phenylhydrazone (5.7 g., 0.025 mole) and diethyl oxalate (0.913 g., 0.00625 mole). The product was recrystallized from 95% ethanol to give 1.55 g. (89%) of **17**, m.p. 233-235°; ir (nujol): 3.17 μ (OH) and 6.04 μ (C=O).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.64; H, 5.24; N, 9.96.

4-Hydroxy-6-phenyl-3-pyridazone (**24**).

This compound was obtained by the above procedures from acetophenone hydrazone (7.70 g., 0.050 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product was crystallized from 25 ml. of 95% ethanol to give 0.56 g. (24%) of **22**, m.p. 265-267°. Recrystallization from 95% ethanol gave an analytical sample, m.p. 266-268°; ir (potassium bromide): 3.00 μ (NH), 3.23 μ (OH), and 5.96 μ (C=O); mass spectrum: (70 eV) m/e (relative intensity), 189 (13), 188 (100, M^+), 187 (5), 160 (12, M-28), 159 (10), 144 (7), 132 (6, M-56), 131 (17, M-57), 129 (4), 104 (7), 103 (20, M-85), 102 (10), 78 (4), 77 (22), 76 (6), 57 (11), and 56 (5).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.29; N, 14.89; m/e 188.0586. Found: C, 63.95; H, 4.30; N, 15.18; m/e 188.0582.

4-Hydroxy-6-(*p*-methoxyphenyl)-3-pyridazone (**25**).

This compound was obtained by the above procedures from *p*-methoxyacetophenone hydrazone (8.21 g., 0.050 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product crystallized from 50 ml. of 95% ethanol to give an analytical sample, m.p. 257-259°; ir (potassium bromide): 3.00 μ (NH), 3.10 μ (OH), and 5.96 μ (C=O); mass spectrum: (70 eV) m/e (relative intensity), 219 (14), 218 (100, M^+), 203 (14), 190 (7, M-28), 174 (11), 161 (6, M-57), 149 (4), 147 (6), 146 (3), 137 (3), 133 (6, M-85), 81 (11), 69 (19), 57 (8), 55 (8), 44 (6), 43 (9), and 41 (11).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84; m/e 218.0691. Found: C, 60.37; H, 4.71; N, 12.48; m/e 218.0685.

General Procedure for Conversion of Oxime to its C(α)-Lithio Derivative and Condensation with Diethyl Oxalate.

To a stirred solution of 0.050 mole of oxime in 100 ml. of THF, which was cooled to 0° under a nitrogen atmosphere, was added during 5 minutes, 62 ml. (0.10 mole) of 1.6 *M* *n*-butyllithium. After 30 minutes, the solution was assumed to contain 0.050 mole of dilithioreactant which was condensed with 0.0125 mole diethyl oxalate dissolved in 100 ml. of THF; addition time 5-10 minutes. After stirring at 0° for 45 minutes to 1 hour, the mixture was acidified with 100 ml. of 3 *N* hydrochloric acid, and the layers were separated. The aqueous layer was neutralized with sodium bicarbonate and extracted with ether. The THF layer and ether extracts were combined, dried with anhydrous magnesium sulfate, filtered and evaporated. The residue was recrystallized from an appropriate solvent as noted.

3,3'-Di-(*p*-tolyl)-5,5'-biisoxazole (**18**).

This compound was obtained by the above procedure from 4-methylacetophenone oxime (7.45 g., 0.05 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product was recrystallized from 95% ethanol and dimethylformamide to give 2.93 g. (74%) of **18**, m.p. 258-260°; ir spectrum (nujol): 6.05, 6.10, and 6.35 μ (C=N and ArH).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.81; H, 5.29; N, 8.77.

3,3'-Diphenyl-5,5'-biisoxazole (**19**).

This compound was obtained by the above procedure from acetophenone oxime (6.75 g., 0.05 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product was recrystallized from 95% ethanol and dimethyl formamide to give 2.77 g., (77%) of **19**, m.p. 269-272°; ir spectrum (nujol): 6.23 μ (C=N and ArH).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 66.66; H, 4.97; N, 8.64. Found: C, 67.00; H, 4.96; N, 8.46.

4,4'-Dimethyl-3,3'-diphenyl-5,5'-biisoxazole (**20**).

This compound was prepared by the above procedure from propiophenone oxime (6.9 g., 0.046 mole) and diethyl oxalate (1.8 g., 0.0115 mole). The product was recrystallized from 95% ethanol to give 0.8 g. of material, m.p. 224-225°, which was not cyclized (via

ir) (nujol): 2.86 μ, 2.98 μ, and 6.12 μ. This material was cyclized with 10 ml. of concentrated sulfuric acid at 0° (23) to give 0.36 g. of 20 (22%) m.p. 209-210° after recrystallization from 95% ethanol and dimethylformamide; ir (nujol): 6.04 μ (C=N and ArH).

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.78; H, 5.15; N, 8.59.

4,5-Dihydronaphtho[1,2-c]-5,5′-biisoxazole (**22**).

This compound was prepared by the above procedure from α-tetralone oxime (8.05 g., 0.05 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product was recrystallized from xylene and dimethylformamide to give 1.62 g. of non-cyclized product, m.p. 329-240° (34%-crude yield). One g. of this material was added to 10 ml. of concentrated sulfuric acid at 0°, stirred for 1 hour, poured on to ice, filtered, washed with water, dried and recrystallized from xylene-dimethylformamide to give 0.45 g. of **22** (50% - from non-cyclized material), m.p. 274-276°; ir (nujol): 6.25 μ (C=N and ArH).

Anal. Calcd. for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.61; H, 4.81; N, 7.93.

3,4-Tetramethylene-5,5′-biisoxazole (**23**).

This compound was prepared by the above procedure from cyclohexanone oxime (5.65 g., 0.05 mole) and diethyl oxalate (1.83 g., 0.0125 mole). The product was recrystallized from 95% ethanol to give 2.46 g. (59%) of **23** m.p. 244-246°; ir (chloroform): 3.37, 3.44, and 3.52 μ (-CH_2) and 6.39 μ (C=N).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47; m/e, 244.1216. Found: C, 68.88; H, 6.49; N, 11.40; m/e, 244.1208.

3,3′-(*p*-Anisoyl)-5,5′-biisoxazole (**21**).

This compound was prepared by a modification of the above procedure. The non-cyclized intermediate **26** 2.63 g. (55%), m.p. 245-249° was isolated and recrystallized from ethanol-benzene-dimethylformamide; ir (nujol): 3.17 μ (OH) and 6.25 μ (C=N and ArH).

Anal. Calcd. for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.24; H, 5.38; N, 7.10.

One g. (0.0026 mole) of **26** was dissolved in 10 ml. of concentrated sulfuric acid at 0°, and the mixture was stirred at this temperature for 1 hour, poured on to ice, filtered, washed with water, dried, and recrystallized from xylene-dimethylformamide to give 0.74 g. (82%) of **21**, m.p. 238-240°; ir (nujol): 6.25 μ (C=N and ArH).

Anal. Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.71; H, 4.71; N, 7.80.

Bioxime (**27**).

This compound was prepared by the above procedure. The non-cyclized intermediate **27** was isolated, 2.17 g. (48%) m.p. 277-279°, even after reflux with 3 *N* hydrochloric acid; ir (nujol): 3.10 μ (OH) and 6.25 μ (C=N and ArH).

Anal. Calcd. for $C_{18}H_{14}F_2N_2O_4$: C, 60.00; H, 3.92; N, 7.75. Found: C, 59.88; H, 4.03; N, 7.35.

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(1) To whom inquiries should be addressed.

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