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The oxidation of 3,4-disubstituted isoxazolin-5-ones with active manganese dioxide leads to the formation of C-C and/or C-N linked coupling products.

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Although a great deal of work has been published (1) concerning the monoelectronic oxidation of phenols, little is known about the analogous reactions of heterocyclic compounds with potential hydroxyl groups. From many substituted pyrazol-5-ones, the so called 4,4'-bispyrazol-5-ones were obtained by chromic acid, organic peroxide or even atmospheric oxygen oxidation (2). Analogous coupling products have been obtained from the 3-keto-2-phenyl-2,3-dihydrothionaphthene (3,4), 3-phenyl-2-(3*H*)benzofuranone (4,5), 2-methyl-, 2-phenyl- (6) and 2-carbethoxy-indoxyl (7). It is also well known that the isoxazolin-5-ones, the tautomeric behaviour of which has already been recognized (8), reduce ammoniacal silver solution (9) and are oxidized by ferric chloride (10). Moreover, heating 3-benzyl-4-phenylisoxazolin-5-one with ferric chloride in alcoholic solution, a product is formed to which a 4,4'-isoxazolone ether structure has been assigned (11). On the other hand, the structure of the 5-isoxazolyloisoxazolone ether has been assigned to the product obtained by oxidation of the 3,4-diphenylisoxazolin-5-one with various oxidants (12).

We report here the results of the oxidation of the 3,4-disubstituted isoxazolin-5-ones (1-6) with active manganese dioxide in dichloromethane solution.

Chart 1

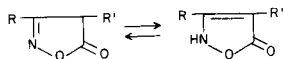


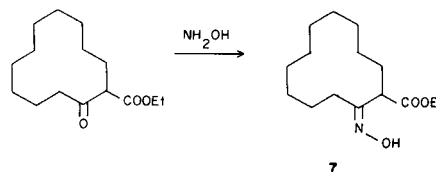
Table 1

R	R'	Compound No.	Reference
Me	Ph	1	18
Ph	Me	2	8a
Ph	Ph	3	12
(CH ₂) ₄		4	8b
(CH ₂) ₁₀		5	(a)
PhCH ₂	Ph	6	11

(a) Present work.

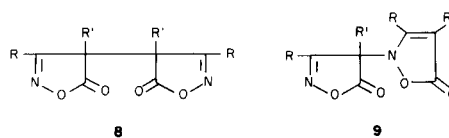
The structure of the hitherto unknown 5 is supported by its synthesis through acid catalyzed cyclisation of the oximino derivative (7) obtained from the 2-carbethoxycyclodecanone (13) and hydroxylamine. Oxidation gives in

Chart 2



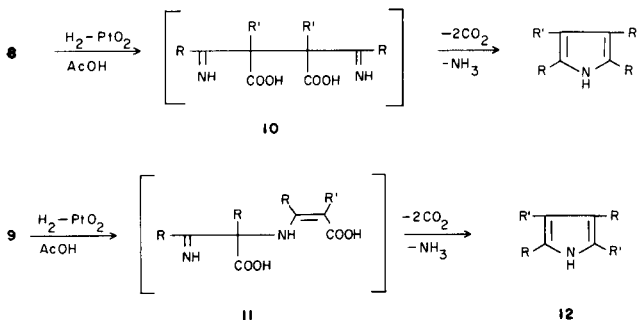
all cases C-C (8) and/or C-N (9) linked coupling products in very good yields. No dimers with C-O bonds between the two isoxazole moieties were detected and C-N derivatives (9) were the main products in the reported examples.

Chart 3



It is known that the catalytic hydrogenation of the isoxazolin-5-ones proceeds through the cleavage of the N-O bond (14). In the case of our dimers (8 and 9), such a reaction [hydrogen-platinum oxide in acetic acid] leads to pyrrole derivatives, arising from the cyclisation of the expected open chain intermediates (10-11). When R ≠ R', this allows the assignment structure 8 or 9 to the starting materials.

Chart 4



Indeed, from 9a, 2,4-dimethyl-3,5-diphenyl pyrrole (12) was obtained, the structure of which was assigned on the basis of analytical and spectroscopic data and by comparison with an authentic sample synthesized from ben-

Table 2

R	R'	Isoxazolin-5-one	Coupling Product	%	ν CO cm^{-1}	λ max nm	M.p. ($^{\circ}\text{C}$)
Me	Ph	1	9a	86.6	1805, 1770	227, 263, 291	123
Ph	Me	2	8a	13.6	1780	252	197
			9b	54	1790, 1760	263	126-127
Ph	Ph	3	9c	90	1820, 1775	222, 266, 295 sh	154
$-(\text{CH}_2)_4-$		4	9d	62.6	1810, 1770	216, 256, 271	161
			8c	15.2	1805	210	196
$-(\text{CH}_2)_{10}-$		5	8d	18.6	1805	210	212
			9e	58	1820, 1760	269	145
PhCH_2	Ph	6	9f	74.3	1800, 1760	230 sh, 276, 294	154.5

zyl methyl ketone and its α -nitroso derivative (15). The same pyrrole (**12**) was obtained from **9b**. From **8a** under these conditions, the known 3,4-dimethyl-2,5-diphenyl pyrrole (16) was formed. Reduction of **9c** afforded the expected 2,3,4,5-tetraphenyl pyrrole (17), but does not allow a choice between the structure **8** and **9**. The structures **9c,d,e,f** as well as **8b,c,d** were assigned on the basis of the comparison of the values of the carbonyl ir absorption with those of **8a** and **9a,b** [see Table 2]. For the derivatives of type **8**, only one absorption band ($1780\text{--}1805\text{ cm}^{-1}$) was present, which is also in good agreement with the reported ir data of the 3,4,4-trisubstituted isoxazolin-5-ones (8d). In the ir spectrum of the derivatives (**9**), two carbonylic absorption bands were present, one in the range $1790\text{--}1820\text{ cm}^{-1}$ and the other at $1760\text{--}1770\text{ cm}^{-1}$. The ^1H nmr and uv data also agree with the assigned structures.

No efforts were made to determine the stereochemistry of the C-C bonded coupling products (**8**). Preliminary studies showed that ^{13}C nmr spectroscopy might be the best method to discriminate between structures **8** and **9**. A complete report on ^{13}C nmr spectroscopy of this type of compounds, together with other oxidation examples and an esr study of the oxidation mechanism will be reported afterward.

EXPERIMENTAL

Ir spectra were recorded on a Perkin-Elmer 377 in nujol; ^1H nmr spectra were recorded in deuteriochloroform solution with a Varian HA 100. Chemical shifts are given in δ from tetramethylsilane as internal standard and refer to the centre of the signal. Uv spectra were recorded for 96% ethanolic solutions on a Beckmann DB GT spectrometer. Mass spectra were recorded with a Varian MAT 311-A mass spectrometer. Column chromatography was performed on Merck Kieselgel 60, 0.063-0.200 mm. Sodium sulphate was used as drying agent. Evaporation was carried out *in vacuo* (rotary evaporator). Melting points were uncorrected. Ethyl 2-Oximinocyclododecanonecarboxylate (**7**).

To a mixture of hydroxylamine hydrochloride (5 g.) and sodium acetate (6 g.) in water (25 ml.), a solution of ethyl 2-cyclododecanone carboxylate (**13**) (10 g.) in ethanol (130 ml.) was added. After heating under reflux for 1.5 hours, the solvent was evaporated, water was added (200

ml.), and the mixture was extracted with dichloromethane ($2 \times 100\text{ ml.}$). The residue resulting from the evaporation of the dried solvent was crystallized from *n*-hexane affording **7** (8.5 g.), m.p. $78\text{--}81^{\circ}$; ir: ν OH 3450 , ν CO 1720 cm^{-1} ; nmr: 7.8 (1H, bs) 3.95 (2H, q, $J = 7\text{ Hz}$) 3.2 (1H, m).

Anal. Calcd. for $\text{C}_{15}\text{H}_{27}\text{NO}_3$: C, 66.88; H, 10.10; N, 5.20. Found: C, 67.11; H, 10.17; N, 5.16.

3,4-Decamethyleneisoxazolin-5-one (**5**).

Hydrochloric acid (2.5N, 20 ml.) was added to a solution of the oximino derivative (**7**) (8.5 g.) in ethanol (120 ml.). After heating for 45 minutes under reflux, the solvent was evaporated, water (150 ml.) was added and the mixture was extracted with dichloromethane ($3 \times 100\text{ ml.}$). The residue from the evaporation of the dried solvent was crystallized from dichloromethane/ether affording **5** (6.5 g.), m.p. $131\text{--}132^{\circ}$; ir: ν NH 3070 (broad), ν CO 1685 , ν C=C 1590 cm^{-1} ; nmr: 3.35 (1H, m); uv: λ max 260 nm (4.04).

Anal. Calcd. for $\text{C}_{15}\text{H}_{27}\text{NO}_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.04; H, 9.36; N, 6.29.

Oxidation of 3,4-Disubstituted Isoxazolin-5-ones (**1-6**). General Procedure.

The isoxazolin-5-one (3 g.) was dissolved in dichloromethane (100 ml.) under nitrogen. Active manganese dioxide (9 g.) was added and the reaction mixture was stirred at room temperature for the reported time. The reaction mixture was filtered on Celite 535, the solvent was evaporated and the residue was crystallized or chromatographed on a silica gel column.

From **1**.

After 12 hours of reaction time, **9a** (2.6 g., 86.6%) was obtained, m.p. 123° (dichloromethane/*n*-hexane); ir: ν CO 1805 , 1770 cm^{-1} ; nmr: 7.5 (5H, s), 7.35 (5H, s), 2.25 (3H, s) 1.81 (3H, s); uv: λ max 227, 263, 291; ms: m/e 348 (M^+) (5), 44 (100).

Anal. Calcd. for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.85; H, 4.66; N, 8.10.

From **2**.

After 2 hours of reaction time followed by column chromatography over silica gel (60 g.) eluant from *n*-hexane to dichloromethane, **8a** was obtained (410 mg., 13.6%), m.p. 197° (ether); ir: ν CO 1780 cm^{-1} ; nmr: 7.5 (10H, s) 2.05 (6H, s); uv: λ max 252 nm ; ms: m/e 348 (M^+) (21), 116 (100).

Anal. Calcd. for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.89; H, 4.64; N, 8.07.

Compound **9b** was also obtained on further elution of the column (1.62 g., 54%), m.p. $126\text{--}127^{\circ}$ (ether); ir: ν CO 1790 , 1760 cm^{-1} ; nmr: 8 (2H, m), 7.5 (8H, m), 1.9 (3H, s), 1.6 (3H, s); uv: λ max 263 nm ; ms: m/e 348 (M^+) (24), 116 (100).

Anal. Calcd. for $C_{30}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.98; H, 4.60; N, 7.99.

From **3**.

After 15 minutes of reaction time, **9c** was obtained (2.7 g., 90%), m.p. 154° (ether/*n*-hexane); ir: ν CO 1820, 1775 cm^{-1} ; uv: λ max 222, 266, 295 sh, ms: m/e 472 (M^+) (2), 44 (100).

Anal. Calcd. for $C_{30}H_{20}N_2O_4$: C, 76.26; H, 4.27; N, 5.93. Found: C, 76.31; H, 4.21; N, 6.01.

From **4**.

After 2 hours of reaction time, **9d** was obtained (1.88 g., 62.6%), m.p. 161° (dichloromethane/ether); ir: ν CO 1810, 1770 cm^{-1} ; nmr: spectrum inconclusive; uv: λ max 216, 256, 271 nm; ms: m/e 276 (M^+) (69), 67 (100).

Anal. Calcd. for $C_{34}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.02; H, 5.81; N, 10.01.

From **5**.

After 1 hour of reaction time followed by column chromatography (90 g., eluant from *n*-hexane to *n*-hexane/dichloromethane 3:1 v:v), **8c** was obtained (456 mg., 15.2%), m.p. 196° (dichloromethane/*n*-hexane); ir: ν CO 1805 cm^{-1} ; nmr: spectrum inconclusive; uv: λ max 210 nm; ms: m/e 444 (M^+) (3), 222 (100).

Anal. Calcd. for $C_{26}H_{40}N_2O_4$: C, 70.23; H, 9.07; N, 6.30. Found: C, 70.71; H, 9.01; N, 6.26.

On further elution of the column, **8d** was obtained (560 mg., 18.6%), m.p. 212° (dichloromethane/ether); ir: ν CO 1805 cm^{-1} ; nmr: spectrum inconclusive; uv: λ max 210 nm; ms: m/e 444 (M^+) (10), 222 (100).

Anal. Calcd. for $C_{26}H_{40}N_2O_4$: C, 70.23; H, 9.07; N, 6.30. Found: C, 70.58; H, 9.03; N, 6.25.

On further elution of the column, **9e** was obtained (1.74 g., 58%), m.p. 145° (dichloromethane/*n*-hexane); ir: ν CO 1820, 1760 cm^{-1} ; nmr: spectrum inconclusive; uv: λ max 269 nm; ms: m/e 444 (M^+) (12), 44 (100).

Anal. Calcd. for $C_{26}H_{40}N_2O_4$: C, 70.23; H, 9.07; N, 6.30. Found: C, 70.15; H, 9.11; N, 6.24.

From **6**.

After 10 minutes of reaction time, **9c** was obtained (2.23 g., 74.3%), m.p. 154.5° (dichloromethane/*n*-hexane); ir: ν CO 1800, 1760 cm^{-1} ; nmr, (pyridine- d_5): 7.15 (20H, m) 4.22 (1H, d, J = 18 Hz), 4.15 (1H, d, J = 16 Hz), 3.88 (1H, d, J = 18 Hz), 3.48 (1H, d, J = 16 Hz); uv: λ max 230 sh, 267, 284 nm; ms: m/e 500 (M^+) (0.1), 91 (100).

Anal. Calcd. for $C_{32}H_{24}N_2O_4$: C, 76.78; H, 4.83; N, 5.60. Found: C, 76.55; H, 4.94; N, 5.59.

Catalytic Reduction of **9a**, **8a**, **9b** and **9c**. General Procedure.

The coupling product (1 mmole) was dissolved in acetic acid (35 ml.) and platinum oxide (50 mg.) was added to the solution. Hydrogenation was then carried out at room temperature under atmospheric pressure until the uptake of hydrogen stopped (ca. 1 hour, ca. 50 ml.). The catalyst was then filtered and the solvent was evaporated. Water (20 ml.) and sodium carbonate (1 g.) were then added and the mixture was extracted with ether (3 \times 20 ml.). The residue of the solvent evaporation was purified by silica gel column chromatography (20 g, eluant *n*-hexane/dichloromethane 1:1 v:v), affording the following products.

From **9a**.

Compound **12** was obtained (140 mg.), m.p. 95-96° (*n*-hexane); ir: 3450,

1600 cm^{-1} ; nmr: 7.8 (1H, bs), 7.33 (10H, m), 2.29 (3H, s), 2.19 (3H, s); ms: m/e 247 (M^+) (100).

Anal. Calcd. for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.02; H, 6.88; N, 5.53.

From **9b**.

Compound **12** was obtained (170 mg.).

From **8a**.

3,4-Dimethyl-2,5-diphenylpyrrole was obtained (210 mg.), m.p. 137° (ether/*n*-hexane) (lit. (16) m.p. 139-139°).

From **9c**.

2,3,4,5-Tetraphenylpyrrole was obtained (200 mg.), m.p. 213° (ether/*n*-hexane) (lit. (17) m.p. 211-212°).

2,4-Dimethyl-3,5-diphenylpyrrole (**12**).

To a solution of benzyl methyl ketone (1.7 g.) and α -nitrosobenzyl methyl ketone (2 g.) in acetic acid (50 ml.), zinc dust (10 g.) and sodium acetate (5 g.) were added. After heating under reflux for 3 hours, the cooled reaction mixture was filtered and the solvent was evaporated. The residue was treated with water (40 ml.) and extracted with ether (2 \times 40 ml.). 2,4-Dimethyl-3,5-diphenyl pyrrole (**12**) was obtained in a pure state by silica gel column chromatography (30 g., eluant *n*-pentane), giving 310 mg. of product, m.p. 96°. Spectroscopic data were identical with those previously reported.

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