OXIDATION OF DIOXOPYRROLINE WITH *m*-CHLOROPERBENZOIC ACID: SELECTIVE FORMATION OF 2,3-DIOXO-1,4-OXAZINE[1]

Takehiro Sano,[a,*] Kazuko Amano,[a] Masaharu Seki,[a] Hiroyuki Hirota,[a] Jun Toda,[a] Fumiyuki Kiuchi,[b] and Yoshisuke Tsuda[b]

Showa College of Pharmaceutical Sciences,[a] 3-3165 Higashi-tamagawa-gakuen, Machida-shi, Tokyo 194, Japan and Faculty of Pharmaceutical Sciences,[b] Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan

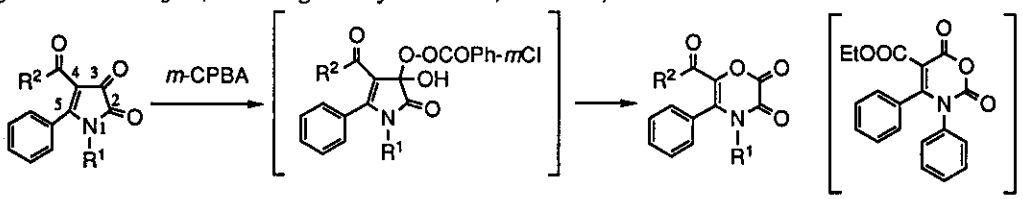
Abstract - Treatment of 4-ethoxycarbonyl-5-phenyl-1*H*-pyrrole-2,3-diones (**1a-1e**) and 4-benzoyl-1,5-diphenyl-1*H*-pyrrole-2,3-dione (**1f**) with *m*-chloroperbenzoic acid caused Baeyer-Villiger oxidation to give 2,3-dioxo-1,4-oxazines (**2a-2f**) in moderate yields, respectively. This conversion of the 1*H*-pyrrole-2,3-dione into the 2,3-dioxo-1,4-oxazine provides the first synthesis of monocyclic 2,3-dioxo-1,4-oxazine ring system.

1*H*-Pyrrole-2,3-dione (dioxopyrroline) has been highly reactive to protic solvents[2] and reductants[3] which gave the products derived from the attack to the C-5 electrophilic center (double bond) of dioxopyrroline. This paper deals with oxidation of dioxopyrroline with *m*-chloroperbenzoic acid (*m*-CPBA), which selectively attacks the C-3 electrophilic center (carbonyl) of the dioxopyrroline to yield a 2,3-dioxo-1,4-oxazine.

Treatment of 4-ethoxycarbonyl-1,5-diphenyl-1*H*-pyrrole-2,3-dione (**1c**) with *m*-CPBA in dichloromethane under reflux gave a 2,3-dioxo-1,4-oxazine (**2c**) as a single product in 66% yield. The molecular weight measured by the mass spectrum (*m/z* 337) indicated that one oxygen was introduced. The high frequency carbonyl absorption at 1783 cm^{-1} observed in the ir spectrum suggested the presence of six membered acid anhydride or enol lactone moiety. The ^{13}C-nmr spectrum clearly showed that the 3-keto carbon of dioxopyrroline had disappeared and instead a new carbon due to -COO- function appeared, thus suggesting the

product to be **2c** or a 2,4-dioxo-1,3-oxazine (**2'**). The 2,3-dioxo-1,4-oxazine structure (**2c**) was finally established by an *X*-ray crystallographic analysis as shown in Scheme 1.

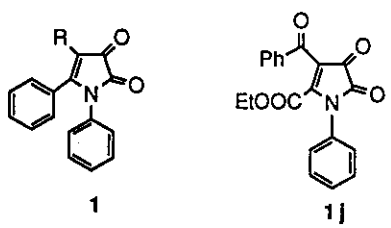
Oxidation of the *N*H (**1a**), *N*-Me (**1b**), *N*-allyl (**1d**), and *N*-benzyl (**1e**) derivatives with *m*-CPBA similarly took place at room temperature to give the 2,3-dioxo-1,4-oxazines (**2a**, **2b**, **2d**, and **2e**) in moderate yields, respectively (Scheme 1). The structures of the products were elucidated by analogy of the spectral data to those of **2c**. Thus, *N*-substituents did not affect the oxidation which only took place at the dioxopyrroline ring. Particularly, it is notable that **1d** gives **2d** in 82% yield, the *N*-allyl group being untouched to any noticeable extent. The formation of 2,3-dioxo-1,4-oxazine was rationalized in terms of Baeyer-Villiger oxidation, where *m*-CPBA attacks the 3-keto group of the dioxopyrroline to form a Criegee adduct and the following ring enlargement due to C_3-C_4 bond migration yields the 2,3-dioxo-1,4-oxazine.



1 **2** **2'**

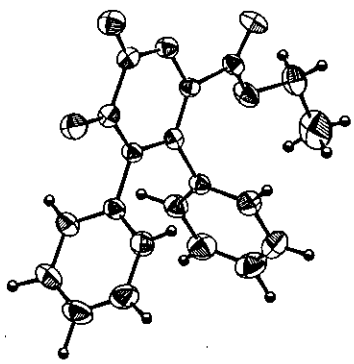
	R^1	R^2
a	H	OEt
b	Me	OEt
c	Ph	OEt
d	CH_2=CH-CH_2	OEt
e	$PhCH_2$	OEt
f	Ph	Ph

	R^1	R^2	Y (%)
a	H	OEt	39
b	Me	OEt	58
c	Ph	OEt	66
d	CH_2=CH-CH_2	OEt	82
e	$PhCH_2$	OEt	73
f	Ph	Ph	51



1 **1j**

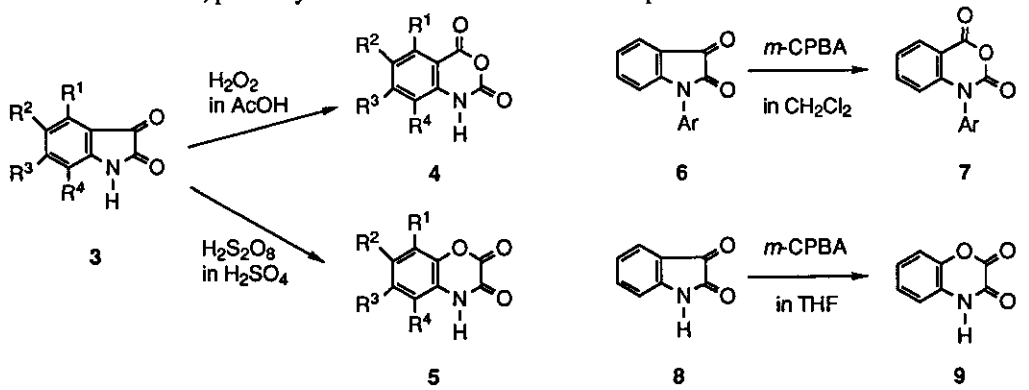
g: R=Me
h: R=Et
i: R=Ph



Scheme 1

Oxidation of several other dioxopyrrolines with different substituents at C-4 and C-5 positions was then examined, which revealed that the oxidation was greatly affected by substituents at C-4. Oxidation of 4-benzoyldioxopyrroline (**1f**) with *m*-CPBA similarly took place at C-3 position of the dioxopyrroline to give the

2,3-dioxo-1,4-oxazine (**2f**) in 51% yield. On the other hand, the 4-methyl (**1g**), the 4-ethyl (**1h**), and 4-phenyl (**1i**) derivatives, hardly gave oxidative product, and the starting material was recovered (30 - 60%) on the reaction in dichloromethane under reflux for several hours. Longer reaction time or higher reaction temperature (reflux in dichloroethane) caused deterioration of the starting dioxopyrroline, and no oxidation product was characterized. Thus, introduction of methyl, ethyl, or phenyl groups at 4-position, compared to ethoxycarbonyl or benzoyl group, decreased the reactivity to *m*-CPBA. The electron releasing group such as alkyl and phenyl should decrease the electrophilic character of the 3-keto group, while the electron withdrawing group such as ethoxycarbonyl group or benzoyl group should increase the electrophilic property of the 3-ketone. 5-Ethoxycarbonyl-4-benzoyl derivative (**1j**) is highly reactive to nucleophilic reagent. On a similar oxidation with *m*-CPBA, the substrate was rapidly consumed as expected. However, no characterizable product was isolated from the reaction mixture, probably due to a further extensive decomposition.

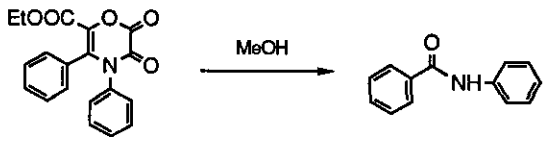


Scheme 2

In Baeyer-Villiger oxidation of isatins, the benzo-analog of dioxopyrroline, the regioselective formation of two possible products by rearrangement of the initially formed Criegee adduct was observed depending on the reaction conditions and oxidizing agent.[4] Oxidation of isatins (**3**) with 30% hydrogen peroxide in glacial acetic acid gave isatoic anhydrides (**4**), 2,4-dioxo-1,3-benzoxazines, while the oxidation with potassium peroxodisulfite in sulfuric acid afforded the isomeric 2,3-dioxo-1,4-benzoxazines (**5**). In the *m*-CPBA oxidation of isatins, the two possible reactions were also observed. The oxidation of *N*-arylisatin (**6**) in dichloromethane regioselectively gave the isatoic anhydride (**7**),[5] while that of NH-isatin (**8**) in tetrahydrofuran regioselectively gave the 2,3-dioxo-1,4-benzoxazine (**9**).[6]

In the oxidation of dioxopyrrolines, the formation of 2,4-dioxo-1,3-oxazine (**2'**) was not observed under similar conditions where isatin gave isatoic anhydride. Oxidation of either *N*H (**1a**) or *N*-Ph (**1c**) with *m*-CPBA in THF

yielded a complex mixture. Furthermore, oxidation of the *N*-Ph derivative (**1c**) with 30% hydrogen peroxide in acetic acid rapidly caused only deterioration of the starting material. Complexity of the product may be due to high reactivity of the dioxopyrroline to protic solvents[2] and that of the formed oxazine under solvolytic conditions. In fact, the *N*-phenyl-2,3-dioxo-1,4-oxazine (**2c**), on treatment with methanol at room temperature overnight, gave benzanilide (**10**) in 63% yield.



2c **10**

Scheme 3

It is worthwhile to note that the above conversion of dioxopyrroline into 2,3-dioxo-1,4-oxazine provides the first synthesis of monocyclic 2,3-dioxo-1,4-oxazine ring system.

EXPERIMENTAL

Unless otherwise stated, the following procedures were adopted. All melting points were taken on a Yanagimoto micro hot-stage melting point apparatus (Yanagimoto MP type) and are uncorrected. Infrared (Ir) spectra were measured with JASCO FT/IR-5000 (KBr disk), and are given in ν_{max} cm^{-1}. Ultraviolet (Uv) spectra were measured with Hitachi U-3200 spectrophotometer in dioxane and given in λ_{max} nm (ε). Nuclear magnetic resonance (Nmr) spectra were taken on JEOL EX-90 (^1H; 90 MHz, ^{13}C; 22.5 MHz) NMR spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. The chemical shifts are given in δ values. Low resolution mass spectra (LRms) and high resolution mass spectra (HRms) were determined with JEOL JMS-D 300 spectrometer at 30 eV or 70 eV by direct inlet system. Dioxopyrrolines (**1a-e**,[7] **1f**,[8] **1g-h**,[9] and **1j**[10]) were prepared by their reported methods, respectively.

Preparation of Dioxopyrroline (1i) A mixture of deoxybenzoin (10 g, 44.6 mmol), aniline (1 mol eq), and *p*-TsOH (100 mg) in toluene (120 ml) was heated under reflux using a Dean-Stark water separator for 18 h. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography over SiO_2 eluting with CH_2Cl_2 to give the crude imine (8.8 g). Oxalyl chloride (1 mol eq) in Et_2O (10 ml) was dropwisely added to a solution of the imine (8.8 g) in Et_2O (10 ml) at 0°C. The reaction mixture was then diluted with anhydrous dioxane (10 ml), and heated at 50°C for 1.5 h. Filtration of precipitates gave **1i** (4.7 g, 24%) as red prisms, mp 253-254°C from benzene. Ir: 1755, 1710, 1600. Uv: 250 (19300), 258 sh (18300), 437 (2500). ^1H-Nmr: 6.90-

7.33 (15H, m, ArH). *Anal.* Calcd for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.31. Found: C, 81.23; H, 4.98; N, 4.29.

Oxidation of Dioxopyrroline (1) with *m*-CPBA (General Procedure) A mixture of dioxopyrroline (**1**) and *m*-CPBA (1.5-4.0 mol eq.) in dry CH_2Cl_2 (50-100 ml) was stirred at room temperature (rt) or refluxed for appropriate times. The reaction mixture was diluted with CH_2Cl_2, and washed with 5% $NaHSO_3$, 5%$NaHCO_3$, and water. After removal of the solvent *in vacuo*, the residue was purified by recrystallizations from ether-CH_2Cl_2 to afford **2**.

2a: The reaction was carried out (rt) with 2.5 mol eq of *m*-CPBA for 2 h. Yield: 39%. Colorless prisms, mp 158-162°C. Ir: 1802, 1754, 1688. ^{1}H-Nmr: 1.04 (3H, t, *J* =7 Hz, $CO_2CH_2C\underline{H}_3$), 4.12 (2H, q, *J* =7 Hz, $CO_2C\underline{H}_2CH_3$), 7.4-7.7 (5H, m, ArH), 8.80 (1H, br s, N$\underline{H}$). ^{13}C-Nmr: 13.9 (q), 61.9 (t), 128.5 (dx2), 129.5 (dx3), 131.9 (s), 132.3 (s), 147.7 (s), 157.5 (s), 158.4 (s), 163.5(s). Uv: 239 (6600), 283 (11200). LRms (*m/z*): 261(M^+), 104 (base peak).

2b: The reaction was carried out (rt) with 1.5 mol eq of *m*-CPBA for 1 h. Yield: 58%. Colorless prisms, mp 162-167°C. Ir: 1781, 1740, 1715, 1700. ^{1}H-Nmr: 1.03 (3H, t, *J* =7 Hz, $CO_2CH_2C\underline{H}_3$), 3.05 (3H, s, NCH_3), 4.05 (2H, q, *J* =7 Hz, $CO_2C\underline{H}_2CH_3$), 7.2-7.6 (5H, m, ArH). ^{13}C-Nmr: 13.6 (q), 33.0 (q), 61.6 (t), 126.4 (s), 129.1 (dx4), 129.7 (s), 130.2 (d), 132.6 (s), 151.5 (s), 151.8 (s), 159.2 (s). Uv: 268 (11900). LRms (*m/z*): 275 (M^+), 118 (base peak). HRms (*m/z*): Calcd for $C_{14}H_{13}NO_5$ (M^+): 275.0792. Found: 275.0777.

2c: The reaction was carried out (reflux) with 1.5 mol eq of *m*-CPBA for 6 h. Yield: 66%. Pale yellow prisms, mp 207-208°C. Ir: 1783, 1719, 1698. ^{1}H-Nmr: 1.02 (3H, t, *J* =7 Hz, $CO_2CH_2C\underline{H}_3$), 4.07 (2H, q, *J* =7 Hz, $CO_2C\underline{H}_2CH_3$), 6.9-7.3 (10H, m, ArH). ^{13}C-Nmr: 13.5 (q), 61.7 (t), 126.4 (s), 127.9 (dx2), 128.6 (dx2), 129.0 (d), 129.1 (dx2), 129.3 (d), 129.4 (s), 130.7 (dx2), 132.8 (s), 135.0 (s), 151.3 (s), 152.0 (s), 159.4 (s). Uv: 266 (14200). LRms (*m /z*): 337(M^+), 180 (base peak). HRms (*m/z*): Calcd for $C_{19}H_{15}NO_5$ (M^+): 337.0933. Found: 337.0931.

2d: The reaction was carried out (rt) with 1.5 mol eq of *m*-CPBA for 18 h. Yield: 82%. Pale yellow prisms , mp 114-115°C. Ir: 1771, 1719, 1690. ^{1}H-Nmr: 1.01 (3H, t, *J*=7 Hz, $CO_2CH_2C\underline{H}_3$), 4.04 (2H, q, *J*=7 Hz, $CO_2C\underline{H}_2CH_3$), 4.11,4.17 (each 1H, dd, *J*=1 Hz, 5 Hz, allyl-H), 4.8-5.9 (3H, m, allyl-H), 7.2-7.6 (5H, m, ArH). ^{13}C-Nmr: 13.6 (q), 47.6 (t), 61.7 (t), 119.4 (t), 126.5 (s), 128.7 (dx2), 129.0 (s), 129.6 (dx2), 130.0 (d), 130.3 (d), 132.4 (s), 151.2 (s), 151.6 (s), 159.2 (s). Uv: 265 (12000). LRms (*m/z*): 301 (M^+), 104 (base peak). HRms (*m/z*): Calcd for $C_{16}H_{15}NO_5$ (M^+): 301.0981. Found: 301.0984.

2e: The reaction was carried out (rt) with 2.0 mol eq of *m*-CPBA for 15 min. Yield: 73%. Pale yellow prisms , mp 118-124°C. Ir: 1783, 1715, 1698. ^{1}H-Nmr: 0.99 (3H, t, *J*=7 Hz, $CO_2CH_2\underline{CH_3}$), 4.01 (2H, q, *J*=7 Hz, $CO_2\underline{CH_2}CH_3$), 4.83 (2H, s, $\underline{CH_2}Ph$), 6.7-6.9 (2H, m, ArH), 7.0-7.5 (8H, m, ArH). ^{13}C-Nmr: 13.6 (q), 48.6 (t), 61.7 (t), 126.6 (s), 127.3 (dx3), 127.9 (s), 128.5 (dx3), 128.8 (dx2), 129.9 (dx2), 130.1 (d), 132.3 (s), 134.7 (s), 151.7 (s),151.9 (s), 159.2 (s). Uv: 266 (13700). LRms (*m/z*): 351 (M^+), 91 (base peak).

2f: The reaction was carried out (rt) with 1.5 mol eq of *m*-CPBA in benzene at room temperature for 4 h and at reflux for 3 h. Yield: 51%. Yellow prisms , mp 253-255°C. Ir: 1774, 1692, 1665. ^{1}H-Nmr: 6.99-7.85 (15H, m, ArH). ^{13}C-Nmr: 128.2 (dx2), 128.4 (s), 128.44 (dx4), 129.1 (d), 129.2 (dx2), 129.5 (d), 129.6 (dx2), 130.6 (dx2, s), 132.8 (s), 133.5 (d), 134.9 (s), 135.8 (s), 151.1 (s),152.1 (s), 185.9 (s). Uv: 257 (13400), 307 (11200). LRms (*m /z*): 369(M^+), 180 (base peak).

***X*-Ray Crystallographic Analysis of 2c** Crystal data: Crystal forms, monoclinic. a=11.347(7), b =6.811(5), c =21.411(4) Å. β=92.83(4)°. V=1653(2) Å^3. D_C=1.356 g/cm^3. Space group $P2_1/n$. Z value 4.

The reflection data were collected on a Rigaku AFC-5R four-circle diffract meter using graphite-monochromated MoK_α radiation in the ω-2θ scan mode at a 2θ scan speed of 6°/min for 3°< 2θ < 55°. Of the reflections (4329) collected, those above the 3$\sigma(I)$ level (1760) were used for the calculation. The structure was solved by the direct method using MITHRIL.[11] R=0.049

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