THE OXIDATION REACTION OF INDOLES WITH THALLIUM(III) TRINITRATE
Takeshi Ohnuma, Hitoshi Kasuya, Youichi Kimura, and Yoshio Ban.*
Faculty of Pharmaceutical Sciences, Hokkaido University,
Sapporo, 060 Japan

Dedicated to Professor Kyosuke Tsuda on the occasion of his 75th birthday

Abstract - Some indole derivatives were submitted to the oxidation
with thallium(III) trinitrate(TTN) to give the corresponding oxindole
and isatin derivatives. Indole-3-propionic acid derivatives were oxi-
dized with TTN to afford the spiro-γ-lactones in good yields.

During the past decade, the investigation of oxidation reaction of olefinic
compounds with thallium(III) reagents has been extensively made by McKillop and
Taylor,¹ who clarified the unique useful properties of this reagent to be unattain-
able with any other oxidizing reagents for organic syntheses. Although oxidation
reactions at C₂,C₃-double bond of indole derivatives for generation of the corre-
sponding oxindoles with a variety of oxidizing agents have been known,² these
methods are not always useful because of low overall yields accompanied by
unfavored by-products under rather drastic conditions.

We describe here the new oxidation method of some indole derivatives with
thallium(III) trinitrate(TTN)³ giving the notable results. Table I summarizes the
conversion of indoles(1, 2, 7, and 8) with TTN into the corresponding C₃-disub-
stituted oxindoles(3, 4, 5, and 6) and isatin derivatives(9 and 10),⁶ while
oxidations of the same compounds performed with Tl(OAc)₃ and Tl(OCCF₃)₃ were not
satisfactory. In the cases of 5 and 6, it was presumed that the nitro group was
introduced to C₃-position of the oxindoles based on their spectral data(5, mp 149-
151°, IR(CHCl₃) 1745 and 1550 cm⁻¹; MS m/e 192(M⁺) and 146(M⁺-NO₂, base peak):
6, IR(CHCl₃) 1730 and 1555 cm⁻¹; MS m/e 278(M⁺) and 232(M⁺-NO₂, base peak)] and
the elemental analyses. The oxidation of oxindole 11 with TTN in methanol at 25°
afforded 3 in a high yield. When this oxidation was conducted in dry acetonitrile
and then treated with water,⁷ a nitrate group was introduced to give the 3-nitroxy-
oxindole 13[mp 110°, IR(CHCl₃) 3200, 1735, and 1640 cm⁻¹; MS m/e 208(M⁺) and 162
(M⁺-NO₂, base peak)], and 12[mp 155-157°(lit ⁸ 161-162°)] as its hydrolyzed product
This new oxidation method of indoles was further applied to the other indole systems having a nucleophilic site such as carboxyl group in the molecules, which afforded the corresponding spirolactone-oxindoles in better yields than by NBS oxidation method \(^9\) (Scheme 2). Oxidative lactonization of the acid 14 with TTN has been already reported to give 15. \(^{10}\) In a similar manner, 16 was submitted to the oxidation [TTN(2.0 equiv), MeOH, -10\(^{\circ}\), 15 min] to furnish 17 (56\%) [mp 160-161\(^{\circ}\), IR(CHCl\(_3\)) 3200, 1780, and 1730 cm\(^{-1}\); \(^1\)H NMR(CDCl\(_3\)) \(\delta\) 2.3-3.5(m, 4), 3.81(s, 3), 6.5-7.3(m, 3) and 8.56(broad, 1, D\(_2\)O exchange); MS m/e 233(M\(^+\))].

Also, the oxidation of N-phthalimide-L-tryptophan (18) with TTN(2.5 equiv)(10\% aq
CH₃CN, 0°→rt, 5 h) gave two diastereomeric lactones, 19a (34%) [mp 271-273°, 
[α]D²⁰ -163° (c 0.5, acetone)]¹¹ and 19b (16%) [mp 261-263°, [α]D²⁰ -220° (c 0.5, 
acetone)],¹² whose stereochemistry at the spiro position was determined by com-
parison with the known optical rotations.¹³ In this oxidation reaction, if the 
reaction time was limited to 5 min under a similar condition (0°), there was read-
ily trapped the intermediate 20 (80%) [mp 239-243° (decomp), [α]D²⁰ -38° (c 0.5, 
acetone); IR(Nujol) 3300, 1780, 1750, and 1720 cm⁻¹; ¹H NMR(DMSO-d₆) δ 5.73 (t, 1, 
J=10 Hz), 7.0-7.4 (m, 4), 7.96 (s, 4), and 11.65 (s, 1); MS m/e 332 (M⁺)], which was 
further treated with TTN in 5% aq CH₃CN to give a mixture of 19a and 19b in 62% 
yield.¹⁴ Further studies are in progress.

Scheme 2
Acknowledgement: This work was financially supported by Grants-in-Aid for Special Project Research "Nitrogen Organic Resources" and for Scientific Research C(No. 557477) from the Ministry of Education, Science and Culture, which is gratefully acknowledged.

REFERENCES AND NOTES


4. The compound 3, mp 120-122°(lit8 121-123°), IR(Nujol) 1745 and 1715 cm⁻¹; ¹H NMR(CDC13) δ 1.60(s, 3), 3.09(s, 3), 6.9-7.3(m, 4), and 9.11(broad, 1, D₂O exchange); MS m/e 177(M⁺).

5. The compound 4, IR(CHC1₃) 3250 and 1720 cm⁻¹; ¹H NMR(CDC1₃) δ 1.20(t, 3, J=7Hz), 2.3(m, 4), 4.09(q, 2, J=7Hz), 4.2(broad, 1, D₂O exchange), 7.2(m, 4), and 8.81(broad, 1, D₂O exchange); MS m/e 249(M⁺).

6. The compounds, 9(IR(Nujol) 1740, 1720, and 1700 cm⁻¹; ¹H NMR(acetone-d₆) δ 2.76(t, 2, J=7Hz), 4.02(t, 2, J=7Hz) and 7.0-7.8(m, 4); MS m/e 219(M⁺) and 132(base peak)], and 10(mp 97.5°, IR(Nujol) 1740 cm⁻¹; ¹H NMR(CDC1₃) δ 2.71(t, 2, J=8Hz), 3.62(s, 3), 3.97(t, 2, J=8Hz), and 6.9-7.6(m, 4); MS m/e 233(M⁺) and 132(base peak)]. Furthermore, the compound 10 was identical with the sample obtained through N-alkylation of isatine with methyl acrylate in the presence of sodium hydride in THF-DME at room temperature.


11. The compound 19a, IR(Nujol) 3250, 1790, 1760, 1745, and 1700 cm⁻¹; ¹H NMR(acetone-d₆) δ 3.11(dd, 2, J=3, 10Hz), 5.71(t, 1, J=10Hz), 7.0-7.6(m, 4) and 7.95(s, 4); MS m/e 348(M⁺)].

12. The compound 19b, IR(Nujol) 3200, 1800, 1770, 1740, and 1710 cm⁻¹; ¹H NMR(DMSO-d₆) δ 2.8-3.2(m, 2), 5.83(dd, 1, J=10, 13Hz), 6.9-7.8(m, 4) and 7.92(s, 4); MS m/e 348(M⁺).


Received, 30th September, 1981

-380-