[Chem. Pharm. Bull. 22(7)1656—1658(1974)]

UDC 547.597.04 : 541.14

Reactions of Enmein-type Compounds with Lead Tetraacetate and Iodine under Irradiation[1]

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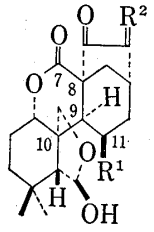
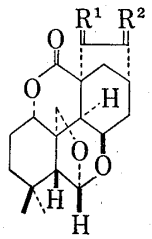
(Received July 28, 1973)

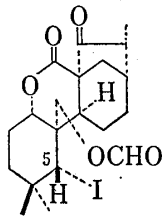
As a potential biogenesis of nodosin (**1**),[3] a minor diterpenoid from *Isodon japonicus* Hara and *I. trichocarpus* Kudo, a route from isodocarpin (**2**)[4] *via* a key-intermediate **4** of isodoacetal (**3**)[5]-type may be assumed. We tried the reaction with lead tetraacetate and iodine under irradiation, so-called hypoiodite reaction,[6] in hopes of the oxygen-functionalization at C-11 of isodocarpine-type compounds, but actually the reactions resulted in the formations of the 5-iodinated 5—6 cleaved product. These findings are reported here.



1: R^1=OH; R^2=CH_2
2: R^1=H; R^2=CH_2
5: R^1=H; R^2=α-CH_3, β-H



3: R^1=α-OAc, β-H; R_2=CH_2
4: R^1=O; R^2=CH_2
6: R^1=O; R^2=α-CH_3, β-H



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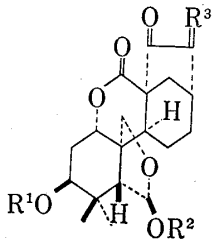
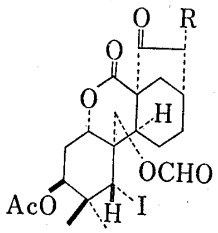
The hypoiodite reaction with the dihydro-derivative (**5**) of isodocarpin gave only a crystalline 5—6 cleaved product **7**, instead of the expected product **6**. The structure of **7**, except the stereochemistry of C-5, was reasonably assigned on the basis of several data shown in the experimental part. The same reaction with dihydroenmein 3-acetate (**9**)[7] also gave the



8: R^1=H; R^2=H; R^3=CH_2
9: R^1=$COCH_3$; R^2=H, R^3=α-CH_3, β-H
11: R^1=$COCH_3$; R^2=H; R^3=α-CH_2OCH_3, β-H
13: R^1=H; R^2=CH_3; R^3=α-CH_2OCH_3, β-H



10: R=CH_3
12: R=CH_2OCH_3

1) This is Part XXX of our Terpenoids series. Part XXIX: M. Shibuya and E. Fujita, *J. C. S. Perkin* I, **1974**, 178.
2) Location: *a) Uji, Kyoto-Fu, 611, Japan; b) 1-chome, Shomachi, Tokushima, 770, Japan.*
3) E. Fujita, T. Fujita, and M. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **16**, 509 (1968).
4) E. Fujita, T. Fujita, and M. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1573 (1968).
5) E. Fujita, M. Taoka, Y. Nagoa, and T. Fujita, *J. C. S. Perkin* I, **1973**, 1760.
6) K. Heusler and J. Kalvoda, *Angew. Chem.*, **76**, 518 (1964).
7) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, H. Irie, A. Numata, T. Fujita, and T. Suzuki, *Tetrahedron*, **22**, 1659 (1966).

fragmentation product **10**, although the yield was low. Isodotricin[8] 3-acetate (**11**) derived *via* **13** from enmein (**8**)[7] on the similar treatment gave product **12** in 68% yield.

The *R*-configuration of C-5 in the products **7**, **10**, and **12** was assigned on the basis of the following observations: (i) In the nuclear magnetic resonance (NMR) spectra, each C-3-H of **10** and **12** was observed as a triplet. The spectra of their materials, **9** and **11**, also showed triplets due to C-3-protons. Furthermore, coupling constants were the same in all cases (Table I). These findings indicate the maintenance of the chair conformation of the ring A through the materials to the products. The compound **7** which has no β-axial acetoxyl group at C-3 must naturally have the stable chair conformation of the ring A. (ii) The protons at C-1 and C-5 of **10** and **12** have lower chemical shifts by 0.33 ppm than those of **7**, respectively. In the compounds **10** and **12**, the C–H bond at C-1 and the C–O bond at C-3 are in relation of 1,3-diaxial. The foregoing observations with the compound **7** tell the same 1,3-diaxial relationship between 5-H and 3β-acetoxyl group in **10** and **12**.

Thus, β-H at C-5, that is, the *R*-configuration of C-5 in these three compounds was clarified.

Table I. NMR Data Used in Discussion

Compound No.	Chemical shifts[a] (shapes,[b] coupling constants) of		
	C-1-H	C-3-H	C-5-H
7	4.34		3.92 (s)
9	4.67 (q, J=11 and 7 Hz)	4.9 (t, J=3 Hz)	
10	4.67	5.13 (t, J=3 Hz)	4.25 (s)
11	4.67 (q, J=11 and 7 Hz)	4.9 (t, J=3 Hz)	
12	4.67	5.15 (t, J=3 Hz)	4.25 (s)

a) δ-Values were shown. *b*) s=singlet, t=triplet, q=quartet

In general, it has been known that the hypoiodite reaction has two courses, that is, the intramolecular abstraction of hydrogen and the fragmentation. In our cases, the undesirable fragmentation of the latter course occurred. The reason why the latter course was prefered may be attributed to the ring strain of the five-membered ring hemiacetal and a stabilization toward the carbonyl formation of the radical initially formed at C-6. Although the examples of the hypoiodite reactions with alcohols have been well known, this may be the first report of the considerably high yield of the fragmentation product in the hypoiodite reaction on hemiacetal.

Experimental

Melting points were taken on a micro hot-stage and are uncorrected. Unless otherwise stated, infrared (IR) spectra were recorded in KBr discs on a Hitachi model EPI-S2 spectrometer and NMR spectra with a varian A-60 spectrometer in deuteriochloroform; signals are reported in ppm from TMS as internal standard. The mass spectra were determined on a Hitachi RMU-6D spectrometer or a JEOL model JMS-OISG double-focusing mass spectrometer.

Hypoiodite Reaction with Isodocarpin Dihydro-derivative (5)——To a suspension of 450 mg of lead tetra-acetate and 150 mg of calcium carbonate in 30 ml of cyclohexane which had been warmed at 60° were added 75 mg of **5** and 80 mg of iodine. The mixture was refluxed under irradiation by 500 W tungsten lamp until the color of the solution disappeared. The filtrate and washing (EtOAc) of the residue were combined and

8) E. Fujita, T. Fujita, Y. Okada, S. Nakamura, and M. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **20**, 2377 (1972).

washed with aq. sodium thiosulfate and water. Evaporation of the solvent *in vacuo* after drying left a residue, which was chromatographed on silica gel column to yield 50 mg of product **7**, mp 228° (from MeOH). *Anal.* Calcd. for $C_{20}H_{27}O_5I$: C, 50.64; H, 5.74; mol. wt., 474. Found: C, 50.47; H, 5.97, Mass Spectrum *m/e*: 474, (M^+). IR ν_{max} cm^{-1}: 1755, 1720, 1180. NMR δ: 8.20 (1H, s, –OCHO), 4.70 (2H, s, C-20 H_2), 4.34 br (1H, t, C-1-H), 3.92 (1H, s, C-5-H).

Hypoiodite Reaction with Dihydroenmein 3-Acetate (9)——A mixture of 1.2 g of lead tetraacetate and 400 mg of calcium carbonate in 80 ml of cyclohexane was warmed to 60°, to which 200 mg of dihydroenmein 3-acetate (**9**) and 214 mg of iodine were added. The mixture was subjected to hypoiodite reaction as described above to yield 60 mg of product **10** after chromatography on silica gel column of the crude product. Recrystallization from MeOH gave the pure compound, mp 195°. *Anal.* Calcd. for $C_{22}H_{29}O_7I$: C, 49.62; H, 5.45; I, 23.87; mol. wt., 532.095. Found: C, 49.48; H, 5.54; I, 23.95, Mass Spectrum *m/e*: 532.098 (M^+). IR ν_{max} cm^{-1}: 1765, 1725, 1230, 1180. NMR δ: 8.19 (1H, s, –OCHO), 5.13 (1H, t, J=3 Hz, C–3–H), 4.67 br (1H, t, C–1–H), 4.25 (1H, s, C–5–H), 2.13 (3H, s, –OAc).

Synthesis of Isodotricin 3-Acetate (11)——A solution of 200 mg of compound **13**[3] in a mixture of each 2 ml of acetic anhydride and pyridine was allowed to stand overnight. Usual treatment of the mixture and purification by chromatography of the crude product gave 162 mg of acetate of **13**, which was refluxed for 4 hr with 60 mg of oxalic acid, 15 ml of water, and 10 ml of MeOH. The mixture, after dilution with water, was extracted with chloroform, and the organic layer was washed with 10% aq. Na_2CO_3 then water. After drying over Na_2SO_4, the solvent was evaporated off *in vacuo* to leave a mixture which was shown to consist of unchanged material and three products by their thin-layer chromatography (TLC) spots. Separation of this mixture through chromatography on silica gel column gave 42 mg of isodotricin 3-acetate (**11**) as an oily substance. *Anal.* Calcd. for $C_{23}H_{32}O_8$: mol. wt., 436.209. Found: Mass Spectrum *m/e*: 436.213 (M^+). IR ν_{max} cm^{-1}: 1760, 1730, 1240. NMR δ: 5.40 (1H, s, C–6–H), 4.90 (1H, t, J=3 Hz, C–3–H), 4.67 (1H, q, J=11 and 7 Hz, C–1–H), 4.01 (2H, s, C–20 H_2), 3.65 (2H, m, C–17 H_2), 3.35 (3H, s, OMe).

Hypoiodite Reaction with Isodotricin 3-Acetate (10)——A mixture of 300 mg of lead tetraacetate and 100 mg of calcium carbonate in 20 ml of cyclohexane was warmed to 60°, to which 50 mg of isodotricin 3-acetate (**10**) and 54 mg of iodine were added. The mixture on hypoiodite reaction and usual treatment of the reaction mixture as described above yielded 34 mg of product **12** as an amorphous substance. *Anal.* Calcd. for $C_{22}H_{31}O_7I$: Mass Spectrum *m/e*: 534.111, (M–CO). Found: 534.112 (M^+–CO). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1730, 1230, 1180. NMR δ: 8.2 (1H, s, OCHO), 5.15 (1H, t, J=3 Hz, C–3–H), 4.67 (2H, s, C–20 H_2), 4.67 br (1H, t, J=8 Hz, C–1–H), 4.25 (1H, s, C–5–H), 3.67 (2H, m, C–17 H_2), 3.35 (3H, s, OMe), 2.13 (3H, s, OAc).

[Chem. Pharm. Bull. 22(7)1658—1660(1974)]

UDC 547.857.7.057

Syntheses of Substituted 8-Aminopurine Derivatives

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(Received September 21, 1973)

In our previous paper[2] it was reported that the condensation of 6-amino-5-nitrosopyrimidines with the Vilsmeier reagents (substituted formamides and phosphorus oxychloride) offers a new route to substituted 8-aminopurine derivatives, and a possible reaction mechanism has been proposed for this condensation. Although the 8-aminopurine-7-oxide is a reasonable intermediate, we could not demonstrate the presence of this intermediate in spite of several efforts. The present paper reports a reaction which suggests the intermediacy of the 8-aminopurine-7-oxide; additionally we wish to describe a conversion of 8-nitropurine derivative to 8-aminopurine derivative using dimethylformamide in the presence of tosyl chloride or phosphorus oxychloride.

1) Location: *Oe-honmachi, Kumamoto.*

2) F. Yoneda, N. Higuchi, T. Matsumura and K. Senga, *Bull. Chem. Soc. Japan*, **46**, 1836 (1973).