On Derivatives of α-Thujaplicin. II. On Nitroderivatives of α-Thujaplicin (o-Isopropyl-tropolone)[1]

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T. Nozoe and his collaborators[2] previously reported the occurence of hinokitiol and its isomer, α-thujaplicin (I) in the acidic constituents of the essential oil of Thujopsis dolabrata, Sieb. et Zucc. ("Hiba"-wood) produced in Aomori Prefecture in Japan. Again T. Nozoe et al.[3] reported on the derivatives of (I), halogen-, nitroso-, amino-derivatives of (I) and *p*-tolyl-azo-dye, etc. The present authors studied nitro-derivatives of (I) and their rearrangement products.

The authors carried out various mono- and di-nitration of (I) with nitric acid, nitrogen peroxide, cupric nitrate and benzoylnitrate. One kind of mononitro-α-thujaplicin m.p. 112–113° (II) and one kind of dinitro-α-thujaplicin 92–93° (III) are obtained. The separation of (III) from (II) is accomplished by adding aniline or *p*-toluidine to a benzene solution of the mixture of (II) and (III), to precipitate a yellow addition compound of (III). Decomposition of the addition compound with acid gives (III). The cupric nitrate method gives a better yield than any other nitration method: that is, the application of three molar equivalents of cupric nitrate to (I) in acetic acid yields (II) (42%) and (III) (21%), in the case of four molar equivalents of cupric nitrate, it yields (II) (30%) and (III) (24%). But when the mix-

1) This work was presented at the 6th Annual General Meeting of the Chemical Society of Japan in Kyoto, April 2, 1953.

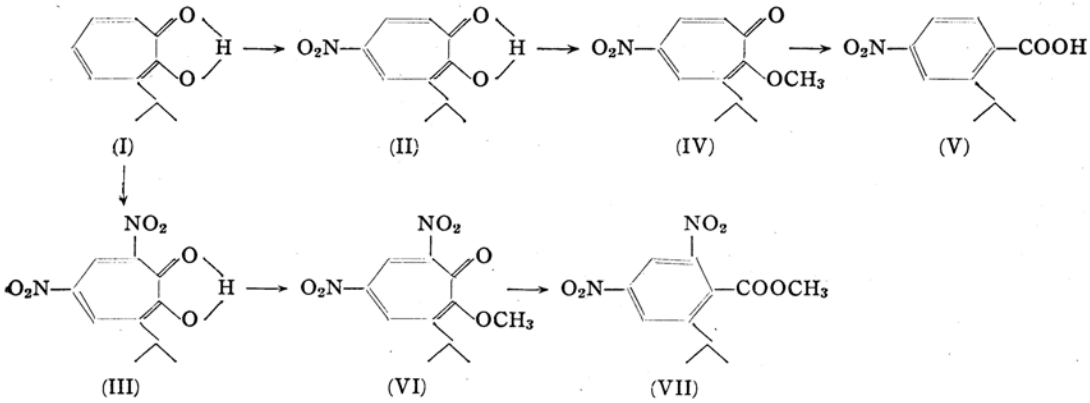
2) T. Nozoe, A. Yasue and K. Yamane, *Proc. Japan Acad.*, **27**, 15 (1951).

3) T. Nozoe, Y. Kitahara K. Yamane, and I. Ikemi, *ibid.*, **27**, 193 (1951).

ture of four molar equivalents of cupric nitrate and (I) in acetic acid is allowed to stand over for five days, (II) (55%) and (III) (14%) are obtained.

The existence of another kind of position isomer of (II) can be considered, but the attempt to find it out during the course of this study was a failure. Moreover, it is noticeable that (II) is unaffected by further nitration with cupric nitrate in an acetic acid solution.

Yellow needles, (II) do not give aniline and *p*-toluidine addition compound but produces a red coloration with ferric chloride. Potassium salt is red prisms, and sodium salt, orange-yellow needles. (II) absorbs three molar equivalents of hydrogen when hydrogenated in methanol with palladium-charcoal as a catalyst, giving amino-α-thujaplicin m.p. 172–173° in a good yield, which is the same substance as that previously obtained by T. Nozoe et al.[3], by the catalytic reduction of the nitroso-derivative and azo-dye of (I). (II) does not couple with the *p*-tolyl-diazonium compound. From these facts and investigations of the substitution reaction of tropolone, hinokitiol and other tropoloides by T. Nozoe et al.[4], the nitro group in (II) is assumed to be at the *p*-position. Methylation of (II) with diazomethane in ether yields a mononitro-α-thujaplicin methylether m.p. 106.2–106.5° (IV) as yellow prisms in a 92% yield. When heated in methanol with sodium methoxide as a catalyst, (IV) undergoes the rearrangement to yield colorless needles m.p. 143–145° (V) in 86% yield, which is assumed to be a mononitro-*o*-cumic acid from the analytical value, the aromatization of other tropoloides and no coloration by ferric chloride characteristic to tropolone nucleus. The determination of the structure of (V) will be reported on the following paper. (V) gives anilide of m.p. 156–156.5°, and *p*-toluidide of m.p. 189°.



(I) (II) (IV) (V)

(III) (VI) (VII)

(III) forms yellow prisms m.p. 92–93°, which give a red coloration by ferric chloride characteristic to tropolone nucleus. (III) is soluble in 2N-potassium hydroxide and sodium hydroxide to give a red coloration, but it soon changes to yellow. (III) does not undergo any rearrangement when heated with alcohol, as dinitrohinokitiol[5] does. With aniline, (III) gives an addition compound of orange-yellow needles m.p. 120–122° (decomp.), which are slightly soluble in benzene. With *p*-toluidine, (III) gives also an addition compound of yellow needles m.p. 152–153° (decomp.), but it changes to orange-red crystals of m.p. 161–162° (decomp.) when left for a long time. *o*-Phenylendiamine addition compound forms yellow needles m.p. 155–156° (decomp.), and phenylhydrazine also gives an addition compound m.p. 104–106° in cold benzene, but does not give phenylhydrazone.

Methylation of (III) with diazomethane in an ethereal solution yields a dinitro-α-thujaplicin methylether m.p. 101–102° (VI) as faintly yellow prisms or needles. (VI) undergoes the rearrangement when heated in methanol with sodium methoxide as a catalyst to yield colorless needles m.p. 97–98° (VII) in a 61% yield, which do not show any coloration with ferric chloride. A trial to obtain the free acid by hydrolysis with 2N-sodium hydroxide without isolating the rearrangement product of (VI) gives colorless prisms m.p. 158–160°, which are assumed to be a mononitro-monohydroxy-*o*-cumic acid from the analytical value, but no detailed studies are made. From the investigations of substitution products of tropolone, hinokitiol and other tropoloides by T. Nozoe et al.[4,5], the nitro groups in (III) are assumed to be at the *o'*- and *p*-position. The determination of the structure of (VII) will be reported later.

Ultraviolet absorption spectra of nitro derivatives of (I) and their rearrangement products are shown in Fig. 1 and 2. (II), (III)

and (IV) have absorption maxima of 350–450 mμ characteristic to tropolone nucleus, while (V) and (VII) have not. It is noticeable that (VI) has also no maximum of 350–450 mμ.

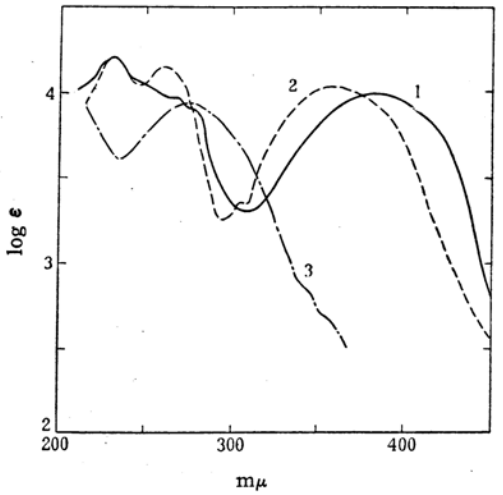


Fig. 1.—Ultraviolet spectra of mononitro-α-thujaplicin (II). (curve 1), mononitro-α-thujaplicin methyl ether (IV), (curve 2), mononitro-o-cumic acid (V), (curve 3) in methanol.

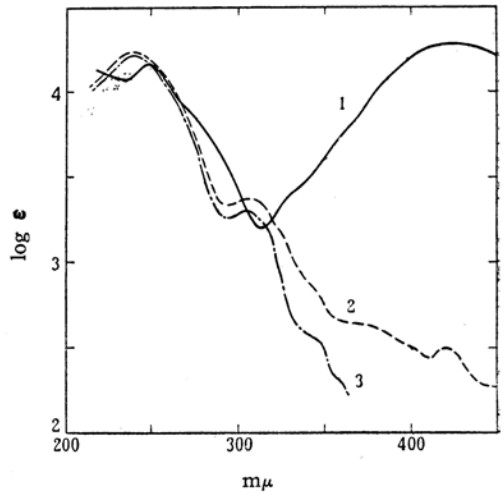


Fig. 2.—Ultraviolet spectra of dinitro-α-thujaplicin (III), (curve 1), dinitro-α-thujaplicin methyl ether (VI), curve 2), dinitro-o-cumic acid methyl ester (VII), curve 3) in methanol.

Experimental

Nitration of α-Thujaplicin (I).

(a) **With Nitric Acid.** 1). To a solution of 1.18 g. of α-thujaplicin (I) in 2 cc. of glacial acetic acid, 0.67g. of sp. gr. 1.42 (68%) nitric acid is added dropwise. The first drop is added at the room temperature, but the subsequent addition is made under ice-cooling during 20 minutes. After the completion of the addition, the mixture is stirred for an hour under ice-cooling, and 0.32g. of yellow crystal of m.p. 105–109° are gained. The recrystallization from benzene gives yellow prisms m.p. 112–113° (II), which give a red coloration with ferric chloride characteristic to tropolones but do not give a p-toluidine compound. Yield 20%. Found: C, 57.12; H, 4.82; N, 7.22, Calculated for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.69%. 2). To a solution of 1.06g. of (I) in 1 cc. of glacial acetic acid, 1.49 g. of sp. gr. 1.42 (68%) nitric acid is added dropwise. The first drop is added at the room temperature, but the subsequent addition is made under ice-cooling during 33 minutes. Yellow crystals begin to separate out after about 10 minutes from the beginning of dropping. After the completion of the addition, the mixture is stirred for an hour under ice-cooling, then the precipitate containing crystals is filtered, and dissolved in benzene and removed from the syrupy matter by decantation. 0.18 g. of (II) are obtained from the benzene solution. Yield 13%. To the filtrate of the precipitation 30 cc. of water is added and the mixture is extracted with benzene. The benzene solution is evaporated to a smaller volume, and aniline is added. Yield, 0.18 g. of an aniline addition compound of (III). Yield of (III), 6%. The recrystallization from benzene gives orange-yellow needles m.p. 118–120° (decomp.). Found: C, 55.38; H, 4.36; N, 11.96, Calculated for $C_{10}H_{16}O_6N_3$; C, 55.48; H, 4.67; N, 12.12%. The decomposition of the addition compound with acid yields (III). The recrystallization from benzene and petroleum ether gives yellow prisms m.p. 92.5–93° (III). Found: C, 47.49; H, 4.04; N, 11.12, Calculated for $C_{10}H_{10}O_6N_2$: C, 47.24; H, 3.96; N, 11.02%.

(b) **With Cupric Nitrate.** To a solution of 2.32 g. of cupric nitrate, $Cu(NO_3)_2 \cdot 3H_2O$, in 5 cc. of glacial acetic acid, a solution of 0.53 g. of (I) in 3 cc. of glacial acetic acid is added dropwise under ice-water-cooling with stirring, and the mixture is left over night in ice-water. To the mixture 25 cc. of water is added, and on standing for an hour, the cupric complex is precipitated. 0.63 g. of the cupric complex is obtained by the filtration, which is decomposed with hot 6N-hydrochloric acid, and extracted with benzene. The benzene solution is evaporated to a smaller volume, and p-toluidine is added, yielding an addition compound of (III.) The recrystallization from benzene gives yellow needles m.p. 152–153° (decomp.). Found: N, 12.21, Calculated for $C_{17}H_{19}O_5N_3$: N, 11.63%. The addition compound of p-toluidine changes to orange-red prisms m.p. 161–162° (decomp.) when left for a long time, and (III) is obtained from both by the decomposition with acid. 0.17 g. of (III) is gained. Yield 21%. From the filtrate of the p-toluidine addition compound of (III), 0.28 g. of (II) is gained. Yield 42%.

Amino-α-thujaplicin. A solution of 0.14 g. of (II) in 25 cc. of methanol is catalytically reduced

4) T. Nozoe, *Science of Drugs*, **3**, 174 (1949); *Sci. Rep. of Tohoku Univ.*, (I), **34**, 199 (1950); T. Nozoe et al., *Proc. Japan Acad.*, **26**, 25, 33. 45 (1950); *ibid.*, **27**, 156, 190, 231. 565 (1951); *ibid.*, **28**, 483 (1952).

5) T. Nozoe, Y. Kitahara, K. Yamane and K. Yamaki, *Proc. Japan Acad.*, **26**, 14 (1950).

with 20 mg. of 5% palladium-charcoal at ordinary temperature and pressure, by which 44 cc. of hydrogen is absorbed. The removal of the catalyst followed by the distillation of methanol gives 0.17 g. of the residue. The recrystallization from benzene and petroleum ether gives yellow prisms, m.p. 172–173°, which do not show any depression of the melting point when fused with amino-α-thujaplicin obtained previously[3] by the catalytic reduction from nitroso-α-thujaplicin and *p*-tolylazo dye of (I).

Mononitro-α-thujaplicin Methyl Ether (IV). To a solution of 0.14 g. of (II) dissolved in a mixture of absolute methanol 5 cc. and absolute ether 10 cc., an etherial solution of diazomethane is added under ice-cooling until the mixture no longer gives a coloration with ferric chloride. The removal of the solvent gives 0.6 g. of crystal m.p. 87–99° by standing over in a vaccum desiccator. Yield 92%. The recrystallization from ether gives yellow prisms (IV) m.p. 105–106°. Found: C, 58.75; H, 5.66; N, 6.12, Calculated for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.87; N, 6.77%.

Rearrangement of Mononitro-α-thujaplicin Methyl Ether (IV). A mixture of 70 mg. of (IV) in a methanolic solution of sodium methoxide, prepared from 20 mg. of sodium and 1.5 cc. of methanol, is refluxed for six hours. To this mixture is added 1 cc. of 2N-hydrochloric acid and the mixture is heated in a water bath for an hour, cooled and filtered. 60 mg. of colorless crystals m.p. 140.5–142.5° are obtained. The recrystallization from 50% alcohol gives colorless needles, m.p. 143–145° (V), which are assumed to be a mononitro-*o*-cumic acid, and does not show any coloration with ferric chloride. Yield 86%. Found: C, 57.86; H, 4.86; N, 6.57, Calculated for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.69%. Anilide of (V) forms colorless prisms m.p. 156–156.5° (from alcohol). Found: N, 9.99, Calculated for $C_{16}H_{16}O_3N_2$: N, 9.86%. *p*-Toluidide of (V) forms colorless needles m.p. 189°. Found: N, 9.40, Calculated for $C_{17}H_{18}O_3N_2$: N, 9.40%.

Addition Compounds of Dinitro-α-thujaplicin (III). Aniline and *p*-toluidine compounds are described above. *o*-Phenylendiamine addition compound forms orange-yellow fine needles, m.p. 155–156° (decomp.) (from alcohol). Found: C, 53.87; H, 4.94; N, 15.00, Calculated for $C_{16}H_{18}O_6N_4$: C, 53.03; H, 5.01; N, 15.41%. Phenylhydrazine addition compound is an orange yellow crystal m.p. 104–106° (decomp.).

Dinitro-α-thujaplicin Methyl Ether (VI). To a solution of 0.13 g. of (III) dissolved in a mixture of absolute methanol 2.4 cc. and absolute ether 7.2 cc., an etherial solution of diazomethane is added under ice-cooling until the mixture no longer gives a coloration with ferric chloride. The removal of the solvent gives 0.087 g. of crystal of (IV) by standing over in a vaccum desiccator. Yield 61%. The recrystallization from methanol gives pale yellow prisms or needles m.p. 99–100° (IV). Found: C, 48.78; H, 4.05; N, 10.17, Calculated for $C_{11}H_{12}O_6N_2$: C, 49.23; H, 4.51; N, 10.45%.

Rearrangement of Dinitro-α-thujaplicin Methyl Ether (VI). (a) A mixture of 48 mg. of (VI) in methanolic solution of sodium methoxide, prepared from 5 mg. of sodium and 1.5 cc. of methanol, is refluxed for six hours. The removal of the solvent gives 36 mg. of colorless scaly crystal m.p. 97–98° (VII). Yield 74%. This crystal is assumed to be a dinitro-*o*-cumic acid methyl ester (VII). Found: C, 49.51; H, 4.55; N, 10.29, Calculated for $C_{11}H_{12}O_6N_2$: C, 49.23; H, 4.51; N, 10.45%. (b) A mixture of 82 mg. of (VI) in a methanolic solution of sodium methoxide, prepared from 5 mg. of sodium and 1.5 cc. of methanol, is refluxed for six hours. After the removal of the solvent, 2 cc. of 2N-sodium hydroxide is added and warmed for two hours in a water bath to effect the hydrolysis. The acidification of the solution with 2N-hydrochloric acid, yields 60 mg. of colorless crystals m.p. 139–150°. The recrystallization from benzene gives colorless prisms m.p. 158–160.5°, which are assumed to be probably a mononitro-monohydroxy-*o*-cumic acid from the analytical value. Found: C, 52.44; H, 4.67; N, 6.79, Calculated for $C_{10}H_{11}O_5N$: C, 53.31; H, 4.92; N, 6.22%.

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