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Some Reactions of Futoxide, a Constituent of *Piper futokadzura* Sieb. et Zucc.[1]

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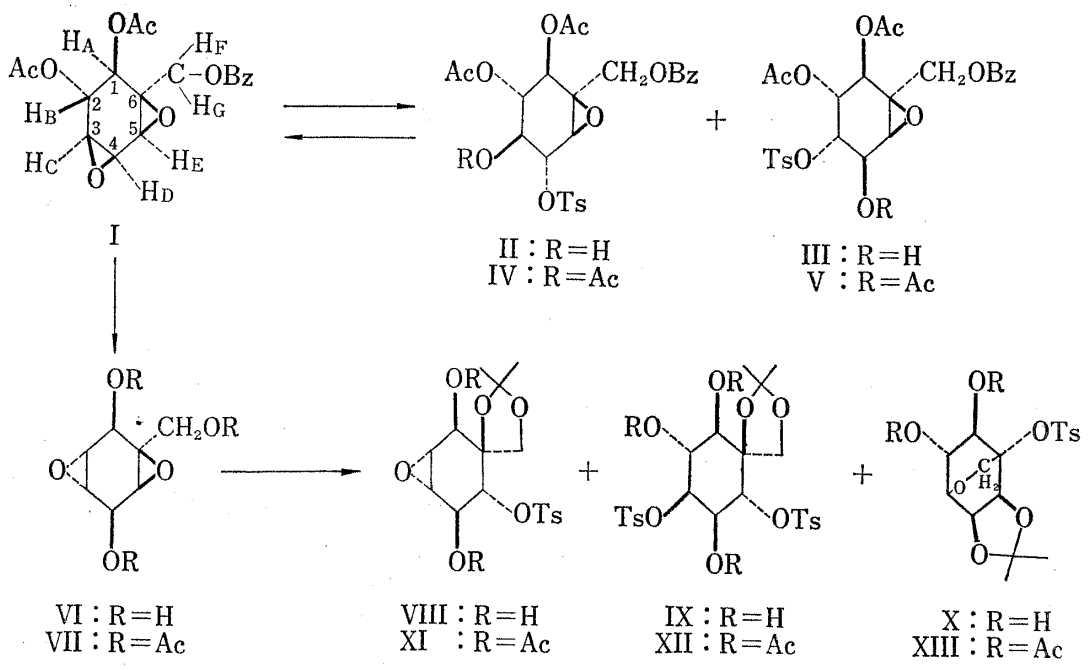
From the leaves and stem of *Piper futokadzura* Sieb. et Zucc., we have isolated a crystalline component designated as futoxide (I), $C_{18}H_{18}O_8$, mp 153°. Kupchan, *et al.* isolated crotepoxide,[3] which showed significant inhibitory activity in Lewis lung carcinoma in mice, from the fruits of *Croton macrostachys* Hochst. ex A. Rich. (Euphorbiaceae). They elucidated the structure of crotepoxide by X-ray analysis of the iodohydrin. Comparison of futoxide with a sample of crotepoxide showed that the materials are identical by mixed melting point, mixed thin-layer chromatography (TLC), and infrared (IR) spectral comparison.[4]

Fotoxide belongs to the group of naturally occurring highly oxygenated cyclohexane derivative.[5] Futoxide, a derivative of 1,3-cyclohexadiene dioxide, was expected to exhibit interesting chemical behavior, although the stereochemical course of epoxide ring opening is well developed.[10]

Treatment of futoxide with *p*-toluenesulfonic acid in acetonitrile gave an isomeric mixture of tosylates (II and III), which regenerated futoxide by treatment with basic alumina. Separation of the tosylate mixture (II and III) was effected by a preparative TLC of acetylated products (IV and V). The structures of the tosyl-acetate (IV), $C_{27}H_{28}O_{12}S$, mp 128—129°, and the isomer (V) were elucidated by the nuclear magnetic resonance (NMR) spectrum shown in Table I. Since the signals due to the proton attached to the carbon bearing *O*-acetyl group generally appear in lower field than those of *O*-tosyl group,[11] supposedly the position of the tosyl group in the tosyl-acetate (IV) is at $C_{(4)}$ while that of the isomer (V) is at $C_{(3)}$. The coupling constants (J_{AB}~9, J_{BC}~10, and J_{CD}~8 cps) of tosyl acetate (IV) are good agreement with the stereochemistry illustrated in structure IV. The isomer (V) is the product formed by the alternative mode of opening the same $C_{(3)}$–$C_{(4)}$ epoxide ring with *p*-toluenesulfonic acid in acetonitrile followed by acetylation.

Hydrolysis of futoxide was carried out by the Zemplén method to afford benzoic acid and triol (VI), $C_7H_{10}O_5$. Spin decoupling experiments of the acetylation product, $C_{13}H_{16}O_8$, mp 67°, of the triol (VI) led to the structure (VII). Irradiation of the peak at 3.10 ppm due to H_B and H_C converts H_A quartet at 5.47 ppm into a singlet, the peak of H_D quartet at 5.35 ppm into a doublet with splitting of 2.8 cps, and H_E at 3.44 ppm which appeared as a quartet by

1) A part of this work has been reported in a preliminary communication: S. Takahashi, *Phytochemistry*, **8**, 321 (1969).
2) Location: *No. 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo.*
3) S.M. Kupchan, R.J. Hemingway, P. Coggon, A.T. McPhail, and G.A. Sim, *J. Am. Chem. Soc.*, **90**, 2982 (1968).
4) The author thanks Professor S.M. Kupchan for the identification of the samples.
5) This members involve shikimic acid, terreic acid,[6] epoxydone,[7] senepoxyde,[8] seneol,[8] and terremutin.[9]
6) J.C. Sheehan, W.B. Lawson, and R.J. Gaul, *J. Am. Chem. Soc.*, **80**, 5536 (1958).
7) A. Closse, R. Mauli, and H.P. Sigg, *Helv. Chim. Acta*, **49**, 204 (1966).
8) R. Hollands, D. Becher, A. Gaudemer, J. Polonsky, and N. Ricroch, *Tetrahedron*, **24**, 1633 (1968).
9) M.W. Miller, *Tetrahedron*, **24**, 4839 (1968).
10) T.W. Craig, G.R. Harvey, and G.A. Berchtold, *J. Org. Chem.*, **32**, 3743 (1967) and references quoted therein.
11) W.E. Truce and A.J. Levy, *J. Am. Chem. Soc.*, **83**, 4641 (1961).

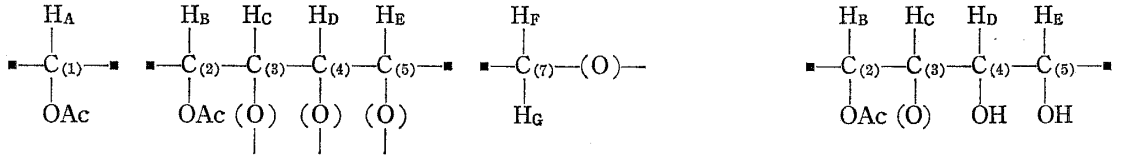


the coupling with H_C into a doublet with the same coupling constant. Migration of epoxide rings is known in sugar chemistry[12] and the migration takes place stereospecifically when a hydroxyl group exists in *trans* relation to the epoxide ring.

On treatment with *p*-toluenesulfonic acid in acetone, the triol (VI) afforded three compounds containing an isopropylidene group (VIII, IX, and X). Acetylation of acetonide (VIII), $C_{17}H_{22}O_8S$, mp 187°, [3500 and 3450 (hydroxyl), 1600 and 1375 cm^{-1} (tosyl)], leading to the acetate (XI), mp 115°, causes a lowfield shift of the signals attributable to H_A and H_D to show peaks at 5.60 and 5.19 ppm respectively. The structure of the acetonide (VIII) was deduced from the NMR data shown in Table I, indicating hydroxyl groups are at $C_{(1)}$ and $C_{(4)}$, and a tosyl group is at $C_{(5)}$. This acetonide (VIII) must be formed by the attack of a tosylate anion at $C_{(5)}$ to open the epoxide ring followed by formation of the acetonide with the primary alcohol at $C_{(7)}$ and the tertiary alcohol at $C_{(6)}$.

The structure of the second acetonide (IX), $C_{24}H_{30}O_{11}S_2$, mp 174°, giving the triacetate (XII), was determined by the NMR data. Thus, this acetonide (IX) was produced by the tosylate anion attack at $C_{(3)}$ from the β-side and at $C_{(5)}$ from the opposite side to open both epoxides.

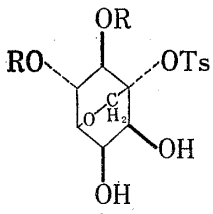
The third acetonide (X) was acetylated to give the diacetate (XIII), $C_{21}H_{26}O_{10}S$, mp 139°. The NMR spectrum shows the presence of two acetyl groups (2.12 and 2.03 ppm), and one tosyl and one acetonide group (1.55 and 1.28 ppm); the following partial structures can be proposed. The structure of the de-O-acetonization product (XIV), mp 141°, prepared by



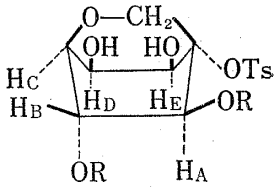
acid treatment of the diacetate (XIII), was postulated by the spin decoupling experiments. Since signals of the two hydroxyl protons appear at 3.76 ppm (J=6.5 cps) and 3.22 ppm

12) J.G. Buchanan, *J. Chem. Soc.*, **1958**, 995; F. Nerdel, G. Barth, D. Frank, and P. Weyerstahl, *Chem. Ber.*, **102**, 407 (1969).

(J=4.3 cps) as a doublet respectively, the hydroxyl groups must be secondary. Furthermore, the secondary alcohols are found to be vicinal each other by the results of decoupling with H_D (4.12 ppm) and H_E (4.53 ppm). All other protons, attached to the carbons bearing oxygen, can be easily assigned as shown in Table I, to deduce the partial structure shown above. The bonds of the oxygens at $C_{(3)}$ and $C_{(7)}$ should be joined to form an ether linkage, because the chemical shifts of the protons H_C, H_F and H_G are too high for a proton affected by a tosylate. In addition to the above results, the observation of nuclear Overhauser effect with H_A and H_E are consistent with the stereochemical structure (XV).



XIV : R=Ac



XV : R=Ac

Results of the epoxide ring opening reactions agree well with the stereochemical structure of futoxide.

TABLE I. The NMR Data of Futoxide and Its Derivatives

	H_A	H_B	H_C	H_D	H_E	$H_{F,G}$
I	5.73 J_{AB}=9.0	5.00 J_{BC}=1.8	3.10 J_{CD}=4.0	3.44 J_{DE}=2.7	3.67	4.23, 4.61 J_{FG}=12.0
IV	5.71 J_{AB}=9.0	5.19 J_{BC}=10.0	5.11 J_{CD}=8.0	4.78 J_{DE}=0.3	3.49	4.48, 4.19 J_{FG}=12.2
V	5.53 J_{AB}=5.5	5.10 J_{BC}=2.0	4.85 J_{CD}=6.5	5.39 J_{DE}=3.0	3.72	4.28, 4.59 J_{FG}=12.0
VII	5.47 J_{AB}=0.7 J_{AC}=0.6	3.10 J_{BC}=0.6	3.10 J_{CD}=0.7	5.34 J_{DE}=2.8	3.45 J_{CE}=1.4	4.30, 4.00 J_{FG}=12.0
VIII	4.09 J_{AB}=2.5 $J_{A\text{-}OH}$=4.5	3.19 J_{BC}=3.5	2.92	3.60 J_{DE}=8.2 $J_{C\text{-}OH}$=6.5	4.82	3.60, 3.68 J_{FG}=10.0
IX	3.57 J_{AB}=9.0 $J_{A\text{-}OH}$=5.0	4.0 J_{BC}=9.8 $J_{B\text{-}OH}$=4 or 10	4.53 J_{CD}=3.2	4.0 J_{DE}=3.2 $J_{D\text{-}OH}$=10 or 4	4.61	4.10, 3.86 J_{FG}=9.5
XI	5.60 J_{AB}=2.5 J_{AC}=1.0	3.25 J_{BC}=3.5	3.08	5.19 J_{DE}=9.0	5.04	3.88, 4.08 J_{FG}=10.0
XII	5.12 J_{AB}=9.5	5.55 J_{BC}=9.5	4.8 m	4.8 m	4.8 m	3.78, 3.98 J_{FG}=9.5
XIII	5.41 s	5.12 J_{BC}=3.5 J_{BD}=0.5	4.24 J_{CD}=1.0	4.33 J_{DE}=7.5	4.94 J_{EF}=1.5	3.98, 4.33 J_{FG}=8.0
XIV	5.45 s	5.12 J_{BC}=4.5 J_{BD}=1.0	4.38 J=1.0	4.12 J_{DE}=5.7 $J_{D\text{-}OH}$=4.3	4.53 J_{EF}=1.5 $J_{E\text{-}OH}$=6.5	F=3.92, G=4.47 J_{FG}=8.0

Chemical shifts are on the δ scale in $CDCl_3$.
s=singlet m=multiplet

Experimental

Treatment of Futoxide with *p*-Toluenesulfonic Acid——A solution of 1.0 g of futoxide and 2.0 g of *p*-toluenesulfonic acid in 10 ml of acetonitrile was allowed to stand for 4 hr at room temperature. The solution was poured into H_2O and extracted with AcOEt. The extract was washed with aq. Na_2CO_3 and H_2O, dried over Na_2SO_4 and evaporated to give 0.8 g of an oil. The crude oil (300 mg) was acetylated in the usual

manner using 6 ml of dry pyridine and 3 ml of Ac_2O to furnish 300 mg of an oily substance. Separation of the oil was effected by a preparative thin-layer chromatography (benzene: AcOEt=4:1) yielding two components. The first was a crystalline acetate (IV), 90 mg, mp 128—129° (from *n*-hexane–AcOEt). *Anal.* Calcd. for $C_{27}H_{28}O_{12}S$: C, 56.25; H, 4.90; S, 5.55. Found: C, 55.89; H, 5.01; S, 5.52. IR ν_{max} cm^{-1}: 1750 and 1745 (ester), 1600 (aromatic), 1370 (tosyl).

The second was an oily acetate (V), 70 mg, showing one spot on TLC (benzene:AcOEt 2:1). IR ν_{max} cm^{-1}: 1750 (ester), 1600 and 1370 (tosyl).

Futoxide from Monotosylates (II and III)——A solution of 30 mg of the tosylates (II and III) in a small amount of AcOEt was placed onto a column of 10 g of basic alumina (Woelm). After standing for 3 hr, the column was eluted with AcOEt. Recrystallization of the product from AcOEt gave crystals, mp 145—151°, which were identified as futoxide by mixed mp, and IR spectra.

Hydrolysis of Futoxide——A solution of catalytic amount of MeONa in 100 ml of MeOH was added to a solution of 2.0 g of futoxide in 100 ml of MeOH. After standing for 4 hr at room temperature, the solution was concentrated and diluted with H_2O. The aqueous solution was eluted through a column of Dowex 50 W (H^+ type). After extraction with ether to remove benzoic acid, the eluent was evaporated to give 1.0 g of an oily triol (VI) which showed one spot on TLC ($CHCl_3$:MeOH=5:1). The triol (VI) was acetylated as usual by using 10 ml of pyridine and 2 ml of Ac_2O to afford the triacetate (VII), which was recrystallized from *n*-hexane–AcOEt to give 0.9 g of crystals, mp 67°. *Anal.* Calcd. for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 51.97; H, 5.24.

Treatment of Triol (VI) with *p*-Toluenesulfonic Acid——A solution of 700 mg of the triol (VI) and 1.0 g of *p*-toluenesulfonic acid in 100 ml of dry acetone was refluxed for 3 days. The resulting solution was concentrated, diluted with H_2O and extracted with AcOEt. After washing with aq. $NaHCO_3$ and H_2O, AcOEt layer was dried over Na_2SO_4 and evaporated to yield a crystalline mass. Recrystallization from AcOEt gave 100 mg of the acetonide (VIII), mp 185—187°. *Anal.* Calcd. for $C_{17}H_{22}O_8S$: C, 52.85; H, 5.74; S, 8.29. Found: C, 52.72; H, 5.76; S, 7.99. IR ν_{max} cm^{-1}: 3500 and 3450 (hydroxyl), 1600 and 1375 (tosyl). The mother liquors were chromatographed on 50 g of silica gel. Elution with benzene–AcOEt (2:1) gave 100 mg of the tosylate (VII). Further elution with benzene–AcOEt (1:1) gave 100 mg of a solid which was recrystallized from *n*-hexane–AcOEt giving the second acetonide (IX), mp 174°. *Anal.* Calcd. for $C_{24}H_{30}O_{11}S_2$: C, 51.61; H, 5.38; S, 11.47. Found: C, 51.20; H, 5.51; S, 11.27. IR ν_{max} cm^{-1}: 3430 (hydroxyl), 1600, 1380 and 1355 (tosyl).

Further elution gave a crystalline substance, mp 160—170°, which was found to be a mixture of the acetonides IX and X.

Acetylation of Tosylate (VIII)——To a solution of 70 mg of the tosylate (VIII) in 2 ml of dry pyridine was added 200 mg of Ac_2O and the solution was allowed to stand overnight. Working-up as usual gave 70 mg of the diacetate (XI) which was recrystallized from *n*-hexane–AcOEt to furnish crystals, mp 113—115°. *Anal.* Calcd. for $C_{21}H_{26}O_{10}S$: C, 53.61; H, 5.57; S, 6.80. Found: C, 53.75; H, 5.69; S, 6.76. IR ν_{max} cm^{-1}: 1755 and 1740 (ester), 1600 and 1375 (tosyl).

Acetylation of the Second Tosylate (IX)——One hundred mg of the second tosylate (IX) was acetylated by the same method mentioned above. The oily acetate revealed one spot on TLC (benzene:AcOEt=4:1).

Acetylation of the Third Tosylate (X)——One hundred mg of the third tosylate (X), containing the second tosylate (IX 30%), was acetylated by the same method mentioned above. The crude acetate was recrystallized from *n*-hexane–AcOEt to give the diacetate (XIII), mp 138—139°. *Anal.* Calcd. for $C_{21}H_{26}O_{10}S$: C, 53.61; H, 5.57; S, 6.80. Found: C, 53.49; H, 5.53; S, 6.76. IR ν_{max} cm^{-1}: 1760 (ester), 1600, 1380 and 1360 (tosyl).

Hydrolysis of the Diacetate (XIII)——A solution of 200 mg of diacetate (XIII) in 10 ml of 50% acetic acid was heated for 4 hr. The resulting solution was diluted with H_2O and extracted with AcOEt. After washing with aq. $NaHCO_3$ and H_2O, the AcOEt solution was dried over Na_2SO_4 and evaporated yielding a crystalline mass. Recrystallization from *n*-hexane–AcOEt gave 100 mg of de-O-acetonide (XIV), mp 141°. *Anal.* Calcd. for $C_{19}H_{22}O_{10}S$: C, 51.58; H, 4.98; S, 7.24. Found: C, 50.00; H, 5.30; S, 7.46. IR ν_{max} cm^{-1}: 3450 (hydroxyl), 1760—1750 (ester), 1600, 1380 and 1360 (tosyl).