[Chem. Pharm. Bull. 20(10)2106—2111(1972)]

UDC 547.597.02 : 581.192 : 615.322.011.5

Studies on Constituents of Medicinal Plants. XI.[1] Constituents of the Roots of *Astilbe Thunbergii* Miquel var. *congests* H. Boissieu

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(Received January 22, 1972)

A new triterpene named astilbic acid (I) has been isolated from the roots of *Astilbe Thunbergii* var. *congests* H. Boissieu (Saxifragaceae) in addition to β-peltoboykinolic acid and the structure of astilbic acid has now been established as 3β,6β-dihydroxyolean-12-en-27-oic acid on the basis of chemical and physicochemical evidences.

There have been some reports regarding the structural elucidation of the constituents of *Astilbe Thunbergii*. Hayashi, *et al.*[3] isolated astilbin and bergenin from the roots and Shimada, *et al.*[4] quercetin from the flowers. This paper deals with the structural elucidation of a new triterpene acid, named astilbic acid. The ethereal extract of the roots, after ether being evaporated, was treated with petr. ether to afford precipitate, from which astilbic acid $C_{30}H_{48}O_4$ (I) of mp 208—209° (decomp.), $[\alpha]^{20}=+100°$ ($c=1.00$, CH_3OH) was obtained. I gave the positive Liebermann–Burchard reaction and afforded monoacetate $C_{32}H_{50}O_5$ (II) of mp 199—201° (decomp.), methylate $C_{31}H_{50}O_4$ (III) of mp 224—226° and acetate methylate $C_{33}H_{52}O_5$ (IV) of mp 286—287°. IV was dehydrated to methyl acetyl anhydro-astilbate $C_{33}H_{50}O_4$ (V) of mp 189—191° and was oxidised to acetyl oxo methylester $C_{33}H_{50}O_5$ (VI) of mp 259—260°. III was oxidised to dioxo methyl ester $C_{31}H_{46}O_4$ (VII) of mp 173—175°. Attempts to hydrogenate of VI by the Wolff–Kishner reduction and to acetylate of IV were unsuccessful. The precipitate, mentioned above, was acetylated and then methylated to give IV and methyl acetyl β-peltoboykinolate.[5] Acetate methylate (IV) exhibits the infrared (IR) bands (cm^{-1}) at 3540 (OH), 1720 (acetate), 1710 (ester), and 825 (trisubstituted double bond). These data suggest that astilbic acid (I) is pentacyclic triterpene monocarboxylic acid with a double bond and two OH groups, one of which is sterically hindered. The COOH group is probably situated in βγ-position to the double bond, because I melts under bubbling. IV shows, on the high resolution mass spectrum (MS), species such as *m/e* 528.369 ($C_{33}H_{52}O_5$, M^+), *m/e* 469.363 ($C_{31}H_{49}O_3$, $M^+-COOCH_3$), *m/e* 497.359 ($C_{32}H_{49}O_4$, M^+-OCH_3), *m/e* 468.355 $C_{31}H_{48}O_3$, M^+-CH_3COOH or $HCOOCH_3$), *m/e* 510.369 ($C_{33}H_{50}O_4$, M^+-H_2O), *m/e* 391.333 ($C_{29}H_{43}$, M^+-CH_3COOH-H_2O-$COOCH_3$), and also *m/e* 262.192 ($C_{17}H_{26}O_2$) and *m/e* 266.190 ($C_{16}H_{26}O_3$), which are characteristic fragmentation ions by the retro Diels-Alder (RDA) fragmentation of amyrin type of triterpene which have a double bond at C_{12}-C_{13}. The MS of IV shows furthermore species *m/e* 248.178 ($C_{16}H_{26}O_3$-H_2O), *m/e* 206.170 ($C_{16}H_{26}O_3$-CH_3COOH), suggesting that the ring A is substituted by a OAc group and the ring B by a OH group or that the ring A by a OH and the ring B by a OAc groups, and also species 203.179 ($C_{17}H_{26}O_2$-$COOCH_3$) and species 202.174 ($C_{17}H_{26}O_2$-$HCOOCH_3$), suggesting that the ring D or E is substituted by a $COOCH_3$ group. The formation of species 302.229 ($C_{20}H_{30}O_2$) from IV is most probably associated with the dehydration, which may be followed by the cleavages of the C_7-C_8 and

1) Part X: K. Takahashi, Y. Hayashi, and M. Takani, *Chem. Pharm. Bull.* (Tokyo), **18**, 421 (1970).
2) Location: *Takaramachi, Kanazawa.*
3) K. Hayashi and K. Ohuchi, *Shigen Kagaku Hokoku*, **17—18**, 19 (1950).
4) G. Shimada, T. Sawada, and S. Fukuda, *Yakugaku Zasshi*, **72**, 578 (1952).
5) M. Nagai, K. Izawa, and T. Inoue, *Chem. Pharm. Bull.* (Tokyo), **17**, 1438 (1969).

C_9-C_{10} bonds by the RDA fragmentation, as 3-oxy-6β-hydroxyolean-12-en-28-oic acid.[6] The nuclear magnetic resonance (NMR) (τ-value) of III, IV, V, and VI exhibit signals as shown in Table I.

Table I. The NMR Data

		III (A)	IV (B)	Δ_1 (B–A)	V	VI	Methyl 3β-acetoxy-β-peltoboykinolate[5] (C)	Methyl 3β-methoxy-β-peltoboykinolate[5] (D)	Δ_2 (C–D)	Δ_3
	C_{28}	9.18(s)3H	9.19(s)3H	0.01	9.18(s)3H	9.16(s)3H	9.17(s)3H[a]	9.14(s)3H[a]	0.03	0
	$C_{29,30}$	9.16(s)6H	9.16(s)6H	0	9.14(s)6H	9.15(s)6H	9.17(s)6H	9.14(s)6H	0.03	0.01
C-CH_3	C_{23}	8.97(s)3H	9.10(s)3H	0.13	8.99(s)3H	9.10(s)3H	9.17(s)3H	9.04(s)3H	0.13	0.13
	C_{24}	8.85(s)3H	8.79(s)3H	−0.06	8.92(s)3H	9.01(s)3H	9.17(s)3H	9.23(s)3H	−0.06	−0.07
	C_{25}	8.73(s)3H	8.74(s)3H	−0.01	8.87(s)3H	8.73(s)3H	9.03(s)3H	9.04(s)3H	−0.01	−0.02
	C_{26}	8.67(s)3H	8.66(s)3H	−0.01	8.83(s)3H	8.96(s)3H	8.90(s)3H	8.98(s)3H	−0.08	0.01
$OCOCH_3$			7.96(s)3H		7.95(s)3H	7.96(s)3H	7.97(s)3H	OCH_3: 6.61(s)3H		
$COOCH_3$		6.37(s)3H	6.37(s)3H		6.42(s)3H	6.28(s)3H	6.34(s)3H	6.30(s)3H		
$C_7{}^{H}_{H}$						7.56, 7.50, 7.46, 7.40 (q) 2H				
C_3H		6.96, 6.88, 6.80 (t, like) 1H $Wh/2$= 16.4 cps	5.66—5.51 (m)2H		5.64—5.48 (q)1H J=6 and 10 cps $Wh/2$= 17 cps	5.71—5.56 (q)1H J=6 and 9 cps $Wh/2$= 16 cps	5.53(t)1H J=7.5 cps			
$\underline{H}C_6$-OH		5.54(m)1H $Wh/2$= 6.4 cps								
$=C_{12}H$		4.39(m)1H	4.39(m)1H		4.43,4.40, 4.36 (t)1H	4.39(m)1H	4.42(t)1H J=2.3 cps	4.34(t)1H J=2.4 cps		
$=C_6H$					4.56, 4.52, 4.47 (t, like)1H					

Δ_1: Differences between effects of OAc and OH groups at C_3 on the C-CH_3 groups of III.
Δ_2: Differences between effects of OAc and OCH_3 groups at C_3 on the C-CH_3 groups of methyl β-peltoboykinolate.
Δ_3: Differences between effects of OAc and OH groups at C_3 on the C-CH_3 groups of β-amyrin.
a) Data measured at 60 Mc, but not assigned by T. Inoue, *et al.*[5]
abbreviation: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet

The NMR signals of trisubstituted olefinic protons at C_{12} of acetate methylates of oleanolic- and ursolic-acids are observed at 4.74 and 4.75, respectively, but that of methyl acetyl β-peltoboykinolate is reported to resonance at 4.42.[5] III and IV exhibit NMR signals of the trisubstituted olefinic protons at 4.39 and 4.39, respectively, suggestnig that III and IV have a trisubstituted olefinic proton at C_{12}-C_{13} and a $COOCH_3$ group at C_{14}, as methyl acetyl-β-peltoboykinolate. The methyl signals of the $COOCH_3$ groups at C_{17} of acetate methylates of oleanolic- and ursolic-acids are observed at 6.445 and 6.465,[7] but those of methyl acetyl β-peltoboykinolate and methyl 3-O-methyl β-peltoboykinolate are reported[5] to resonance at 6.34 and 6.30, respectively. III and IV exhibit the NMR signals of the methyl groups of the $COOCH_3$ groups at 6.37 and 6.37, respectively, suggesting that III and IV have a COO-CH_3 group at C_{14}, as methyl β-peltoboykinolate. Acetate methylate (IV) exhibits also the NMR signals of two protons of $\underline{H}$C-OH and $\underline{H}$C-OAc groups at 5.51—5.56 (m, 2H), but methylate (III) a triplet-like signals at 6.88 (centre, 1H, $W_{h/2}$=16.4 cps) and a multiplet at 5.54

6) I. Wahlberg and C.R. Enzell, *Acta Chem. Scand.*, **25**, 70 (1971).
7) M. Shamma, R.E. Glick, and R.O. Mumma, *J. Org. Chem.*, **27**, 4512 (1969).

(centre, 1H, $W_{h/2}$=6.4 cps), suggesting that astilbic acid (I) has a β-OH (equatorial)[8] group at C_3, and a β-OH (axial) group at C_6 or α-OH (axial) group at C_7.[9]

The pattern of the NMR signals of the methyl groups of III, IV, V, and VI (Table I) suggest that astilbic acid (I) is β-amyrin type of triterpenoid. In view of these spectral evidences and the occurrence of β-peltoboykinolic acid in this plant, astilbic acid (I) is probably 3β, 6β (or 7α) dihydroxyolean-12-en-27-oic acid. The structure of I was elucidated as follows: It is well known that for triterpenoid skeleton,[10,11] modifications in substituent pattern are accompanied by systematic change in the NMR chemical shifts of the neighbouring angular methyl groups, but not of remote methyl groups and that the shielding effects of OH and OCH_3 groups are nearly equal in some cases.[12,13] Such changes are, to a first approximation, additive. In comparison of chemical shift positions of the angular methyl groups[10] of β-amyrin with those of methyl oleanolate, methyl ursolate, it could be deduced that the $COOCH_3$ groups (β, axial) at C_{17} of the latter compounds give the paramagnetic effects (0.21—0.23 ppm) on the methyl groups (β, axial) at C_8 of α and β-amyrin. The molecular model suggests that an introduced $COOCH_3$ group (α, axial) at C_{14} of β-amyrin could contrarily be expected to give the diamagnetic effect on the methyl group (β, axial) at C_8 of β-amyrin type of compound by the anisotropy. Accordingly, the methyl group (β, axial) at C_8 of methyl acetyl- and methyl O-methyl-β-peltoboykinolates could be expected to resonance at lower field than the methyl group (9.04)[10] at C_8 of β-amyrin acetate. On considering the evidences mentioned above, the signals of the angular methyl groups of methyl acetyl and methyl O-methyl β-peltoboykinolate which were reported, but not assigned, could be analysed as shown in Table I. The differences Δ_1, Δ_2, and Δ_3 in Table I were nearly equal and the shielding effects of the $COOCH_3$ group at C_{14} on the methyl groups at C_8 of methyl acetyl- and methyl O-methyl-β-peltoboykinolates were calculated as −0.14 ppm (8.90—9.04[10]) and −0.14 ppm (8.98—9.04—0.08), respectively. There have been some reports regarding the shielding effects of a OH group at C_6[6,10] and C_7[10] on the methyl signals of triterpenoids and steroids. Using these data,[10] methyl 3β-acetoxy-6β-hydroxyolean-12-en-27-oate (methyl 3β-acetoxy-6β-hydroxy-β-peltoboykinolate) could be expected to exhibit the methyl signals of C_{23}, C_{24}, C_{25}, and C_{26} at τ-values as shown in Table II, which are nearly equal to those of the methyl signals of methyl acetyl astilbate (IV), respectively. The methyl signals of IV (8.79, 8.74, 8.66) in rather low field suggest that these methyl groups are in 1,3-diaxial relation[14] to the OH group at C_6 and they could be assigned to the methyl signals of C_{24}, C_{25}, and C_{26} (axial), respectively. 7α-Hydroxy compound could be expected to exhibit the methyl signals at τ-values as shown in Table II, which are different from those of IV. S. Huneck and J.M. Lehn[15] have reported on the substitution effects of 6-oxo group on the methyl groups of hopane type of compounds. Using these data, methyl 3β-acetoxy-6-oxo-olean-12-en-27-oate (methyl 3β-acetoxy-6-oxo-β-peltoboykinolate) could be expected to exhibit the methyl signals at τ-values as shown in Table II, which are nearly equal to those of the methyl signals of acetyl oxo methyl ester (VI). Methyl acetyl anhydro-astilbate (V) exhibits the NMR signals of the proton at C_6 at 4.52 (triplet-like, 1H, J=5 cps) and species *m/e* 208 and *m/e* 302 and furthermore *m/e* 148 (208-CH_3COOH) and *m/e* 243 (302-$COOCH_3$), indicating that V has a double bond at C_5-C_6.

8) K. Tori and T. Komeno, *Tetrahedron*, **21**, 326 (1965).
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10) H.T. Cheung and G.H. Williamson, *Tetrahedron*, **25**, 119 (1969).
11) S. Ito, M. Kodama, M. Sunagawa, T. Oba, and H. Hikino, *Tetrahedron Letters*, **34**, 2905 (1969).
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13) W.H. Hui, K. Luk, H.R. Arthur, and S.N. Loo, *J. Chem. Soc.* (*C*), **1971**, 2826.
14) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).
15) S. Huneck and J.M. Lehn, *Bull. Chim. Fr.*, 1702 (1963).

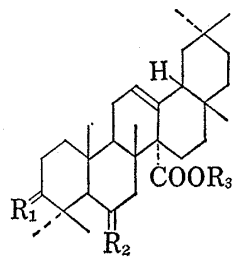
Table II. The NMR Data

C–CH_3	Methyl-3β-acetoxy-β-peltoboykinolate[5]	Effect of 6β-OH on C-CH_3 groups[10]	Methyl-3β-acetoxy-6β-hydroxy-β-peltoboykinolate Calcd. (A)	IV (B)	Δ_{B-A}	Effect of 7α-OH on C–CH_3 groups[10]	Methyl 3β-acetyoxy-7α-hydroxy-β-peltoboykinolate Calcd. (C)
C_{23}	9.17	−0.08[a]	9.09	9.10	0.01	0.02[a]	9.19
C_{24}	9.17	−0.39[b] −0.30[a]	8.78 8.87	8.79	0.01 −0.08	−0.02[a]	9.15
C_{25}	9.03	−0.38[b] −0.27[a]	8.65 8.76	8.74	0.09 −0.02	0.02[a]	9.05
C_{26}	8.90	−0.32[b] −0.30[a]	8.58 8.60	8.66	0.08 0.06	0[a]	8.90

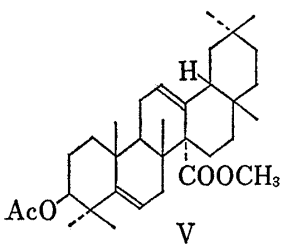
	Δ_{B-C}	Effect of 6-oxo group on C–CH_3 groups[15]	Methyl 3β-acetoxy-6-oxo-β-peltoboykinolate Calcd. (D)	VI (E)	Δ_{E-D}
C_{23}	−0.09	−0.04—0	9.13—9.17	9.10	−0.03——0.07
C_{24}	−0.36	−0.11——0.06	9.06—9.11	9.01	−0.05——0.10
C_{25}	−0.31	−0.42——0.37	8.61—8.66	8.73	0.12— 0.07
C_{26}	−0.24	0	8.90	8.96	0.06

a) The values (ppm) are those for steroids.[10]
b) The values (ppm) are those for triterpenoids.[10]

These evidences indicate that astilbic acid (I) is 3β,6β-dihydroxy-olean-12-en-27-oic acid and so I, II, III, IV, V, and VI could be formulated as shown in Chart 1 and their NMR spectra could be analysed as shown in Table I.



I : R_1=<OH/H, R_2=<OH/H, R_3=H
II : R_1=<OAc/H, R_2=<OH/H, R_3=H
III : R_1=<OH/H, R_2=<OH/H, R_3=CH_3
IV : R_1=<OAc/H, R_2=<OH/H, R_3=CH_3
VI : R_1=<OAc/H, R_2=O, R_3=CH_3
VII : R_1=R_2=O, R_3=CH_3
β-peltoboykinolic acid : R_1=<OH/H, R_2=<H/H, R_3=H



V

Chart 1

Experimental

Melting points were taken in a Kofler-type hot plate and uncorrected. The IR spectra were taken in KBr pellet with Nippon Bunko DS-402G spectrometer, the NMR in $CDCl_3$ with a Varian Associstes NMR spectrometer at 100 Mc with $(CH_3)_4Si$ as internal reference, the optical rotation at 589 mμ with Nippon Bunko automatic polarimeter DIP-SL and the MS spectra with JMS-O1SG mass spectrometer.

The Extraction of the Constituents of the Roots——(i) Dried powder (700 g) of Astilbes radix was extracted with ether for 3 days and after ether being evaporated, the extract was treated with petr. ether to give orange yellow precipitate (1.5 g), two grams of which were chroamtographed over Kieselgel (350 g) with $CHCl_3$–CH_3OH (40:1) as eluent. The eluate from Nos 351 to 381 (17 g each) gave colorless crystalline powder (I) of mp 208—209° (decomp.) from CH_3OH. Yield: 180 mg. Liebermann-Burchard reaction: red-violet-green. *Rf*: 0.23 (Kieselgel, $CHCl_3$: CH_3OH=20:1). *Anal.* Calcd. for $C_{30}H_{48}O_4$: C, 76.05; H, 10.28. Found: C, 76.22; H, 10.24.

(ii) 1.6 g of orange yellow precipitate mentioned above, was acetylated with pyridine (2 ml) and acetic anhydride (10 ml) at 80° for 1 hr and the crude acetate was methylated with diazomethane and then the product was chromatographed over Kieselgel (260 g) with benzene–ethyl acetate (15:1) as eluent. The eluate from Nos 30 to 37 (12 g each) gave methyl acetyl β-peltoboykinolate[5] of mp 207° from CH_3OH. *Rf*: 0.55 (benzene: ethyl acetate=19:1). $[\alpha]^{25}=+132°$ (c=1.0, $CHCl_3$). IR: 1740, 1250 (OAc), 1725 ($COOCH_3$). *Anal.* Calcd. for $C_{33}H_{52}O_4$: C, 77.29; H, 10.22. Found: C, 77.40; C, 10.18. It was proved to be identical with the authentic sample of methyl acetyl β-peltoboykinolate[16] by the mixed fusion and IR. The eluate from Nos 72 to 80 gave acetyl methyl astilbate (IV) of mp 286—287° from CH_3OH.

Acetylation of I——A solution of I (50 mg) in a mixture of pyridine (1.5 ml) and acetic anhydride (10 ml) was kept at room temperature for 24 hr and the solution was poured into dil. HCl–ice water to give colorless crystalline powder (II) of mp 199—201° (decomp.) from benzene. *Rf*: 0.39 ($CHCl_3$: CH_3OH=30:1). IR: 3400 (OH), 1715 (OAc, shoulder), 1708 (COOH), 825 (trisubstituted double bond). *Anal.* Calcd. for $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.69; H, 9.65.

Methylation of I——Fifty milligram of I in ether (20 ml) was methylated with diazomethane to give colorless crystalline powder (III) of mp 224—226° from CH_3OH–H_2O. *Rf*: 0.40 (benzene: ethyl acetate=4:1). IR: 3440 (OH), 1710 (ester), 825 (trisubstituted double bond). *Anal.* Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.22; H, 10.30.

Methylation of II——II (40 mg) was methylated with diazomethane to give colorless needles (IV) of mp 286—287° from CH_3OH. *Rf*: 0.61 (benzene:ethyl acetate=10:1). *Anal.* Calcd. for $C_{33}H_{52}O_5$: C, 74.96; H, 9.91. Found: C, 74.89; H, 9.84.

Oxidation of III——To a solution of III (30 mg) in pyridine (1 ml), CrO_3–pyridine mixture (250 mg CrO_3 in pyridine 6 ml) was added and the mixture was agitated for 2 hr at room temperature and then kept at room temperature for 24 hr. The mixture was extracted with ether and the ether was evaporated to give colorless needles (VII) of mp 173—175° from CH_3OH. Yield: 25 mg. IR: 1718 ($COOCH_3$, shoulder), 1708 (C=O). *Anal.* Calcd. for $C_{31}H_{46}O_4$: C, 77.13; H, 9.61. Found: C, 77.06; H, 9.78.

Oxidation of IV——A mixture of IV (100 mg) in pyridine (2 ml) and pyridine–CrO_3 (307 mg CrO_3 in pyridine 12 ml) was stirred at room temperature for 3 hr and the mixture was ketp at room temperature for 24 hr and then the mixture was poured into dil. HCl–ice water and was extracted with ether. The ether extract gave colorless needles (VI) of mp 259—260° from CH_3OH. *Rf*: 0.48 (benzene–ethyl acetate=13–1). IR: 1723 (OAc), 1715 (ester), 1708 (C=O). *Anal.* Calcd. for $C_{33}H_{50}O_5$: C, 75.24; H, 9.57. Found: C, 75.22; H, 9.45.

Dehydration of IV——IV (330 mg) in pyridine (15 ml) and $POCl_3$ (2 ml) was warmed at 60—70° for 4 hr and the mixture was poured into ice water to give precipitate, which was recrystallysed from CH_3OH to give colorless needles (V) of mp 189—191°. IR: 1740 (OAc), 1715 (ester). *Anal.* Calcd. for $C_{33}H_{50}O_4$: C, 77.60; H, 9.87. Found: C, 77.56; H, 9.84.

Attempt to Acetylate IV——(i) A mixture of IV (50 mg) in acetic anhydride (10 ml) and p-toluene sulfonic acid (25 ml) was kept at room temperature for 24 hr and the mixture was poured into ice water to give precipitate, from which V of mp 191—192° and unchanged IV of mp 286—287° were obtained.

(ii) Acetyl chloride (1.5 ml) was carefully added to a stirred solution of IV (75 mg) in N,N-dimethylaniline (2.5 ml) kept at 0°. The reaction mixture was stirred for one hr at 0° and left at room temperature for 24 hr and then poured into ice water and extracted with ether. The ether extract, after ether being evaporated, was chromatographed over Kieselgel (12 g) with benzene–ethyl acetate (30:1) to give methyl acetyl dehydro-astilbate (V) of mp 190—192° (35 mg) (mixed fusion and IR comparison), but diacetyl methyl astilbate was not obtained.

Attempt to reduce VI by Wolff-Kishner Method——A mixture of VI (60 mg), n-butylcellosolve (8 ml), diethylene glycol (2 ml), $NH_2NH_2H_2O$ (3 ml) and NH_2NH_2HCl (180 mg) was refluxed at 140° for 4 hr and

16) The sample was furnished through the courtesy of Prof. Dr. T. Inoue of Hoshi College of Pharmacy.

then KOH (0.6 g) and diethylene glycol (2 ml) was added and then the temperature of the mixture rised to 180°, while distilling off the excess of $NH_2NH_2H_2O$ and H_2O. After a further 5 hr at this temperature, the reaction mixture was cooled and extracted with ether. The ether layer gave a substance, which was acetylated with acetic anhydride and pyridine and then methylated with diazomethane to give colorless crystals of mp 259—260° from CH_3OH–H_2O. It was proved to be identical with the starting material (VI) by mixed fusion and IR, TLC comparison.

Acknowledgement The authors are deeply indebted to Prof. T. Inoue of Hoshi College of Pharmacy for the sample of acetyl methyl β-peltoboykinolate. The authors wish to thank to the Research Laboratory of Takeda Chemical Industries and Mr. Y. Itatani for measurement of NMR spectra and to Miss T. Tuji for measuring Mass spectra and to Mr. Y. Itatani and Miss S. Toyoshima for elemental analyses.