Alangiside, the Monoterpenoid Alkaloidal Glycoside from *Alangium lamarckii* Thw.[1]

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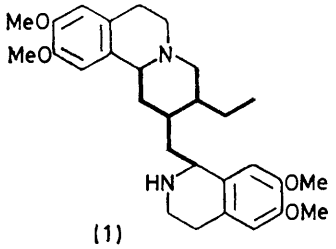
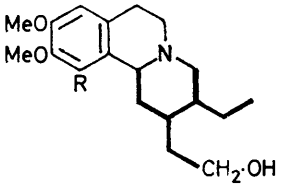
The structure and absolute configuration of *O*-methylalangiside (15) {11-(β-D-glycopyranosyloxy)-5,11,12,-12a,13,13a-hexahydro-2,3-dimethoxy-12-vinyl-6*H*-benzo[*a*]pyrano[3,4-*g*]quinolizin-8-one} has been established by chemical and spectroscopic studies and by correlation with ipecoside. Synthetic evidence is presented which indirectly confirms the 3-methoxy- (11) rather than the 2-methoxy-structure (12) for alangiside.

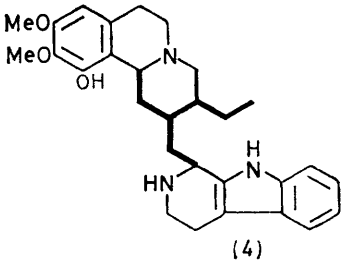
Alangium lamarckii Thw. (Alangiaceae) is a medicinal plant indigenous to India and is a rich source[2,3] of alkaloids structurally related to the Ipecac bases, *e.g.* emetine (1). The isolation of dihydroprotoemetine (2),



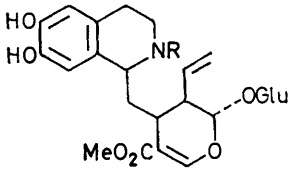
(1)



(2) R = H
(3) R = OH



(4)

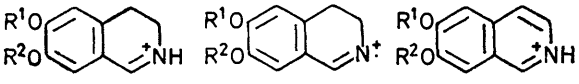


(5) R = Ac
(6) R = H

ankorine (3),† and alangimarckine (4) added further interest to the chemical examination of this plant. The presence of the now familiar C_{9-10} unit (shown as thickened bonds) derived presumably from loganin in all these structures led us to a search for the monoterpenoid glycosidic precursor[1,4] predicted by biogenetic theory.

An extraction and isolation of the glycosidic fraction was accordingly undertaken on the lines described for the case of ipecoside[5] (5). A brown amorphous powder was obtained which on purification by a combination of counter-current distribution and column chromatography gave a white amorphous powder shown to be pure by t.l.c. in two solvent systems and named alangiside.

Alangiside could be isolated from the roots, leaves, or fruit of *A. lamarckii* (best source unripe fruit). Its molecular formula, $C_{25}H_{31}NO_{10}$, was confirmed by mass spectrometric study of the compound itself and of four derivatives. Its u.v. spectrum [$\lambda_{max.}$ (MeOH) 237 and 285 nm (log ε 4·27 and 3·68)], which underwent a bathochromic shift in alkali ($\lambda_{max.}$ 247 and 303 nm) was similar to that of ipecoside.[6] The i.r. spectrum indicated the presence of OH ($\nu_{max.}$ 3 350br cm^{-1}) and only one carbonyl group (1 650 cm^{-1}). The n.m.r. spectrum showed signals at τ 6·21 (OMe), 4·60 (3H, m, olefinic), 3·25 (2H, m, aromatic), 2·61 (1H, d, O=C–C=C*H*–O). The mass spectrum showed a weak M^+ peak at *m/e* 505 and a stronger peak at *m/e* 343 (aglucone). The base peak was at *m/e* 274 (retro-Diels–Alder from M^+) and there were other prominent peaks at *m/e* 272, 178, 177, and 176, the last three corresponding to the ions (7)—(9), respectively. The appearance of these



(7) R^1 = H, R^2 = Me or R^1 = Me, R^2 = H

(8) R^1 = H, R^2 = Me or R^1 = Me, R^2 = H

(9) R^1 = H, R^2 = Me or R^1 = Me, R^2 = H

characteristic peaks in the mass spectrum of alangiside and its derivatives (see later) and the presence of dihydroprotoemetine, ankorine, and other benzoquinolizidine alkaloids in this plant pointed to the presence of a common benzoquinolizidine unit.

β-Glucosidase cleaved alangiside to yield D-glucose and the aglucone, $C_{19}H_{21}NO_5$. The mass spectrum of the aglucone showed ions at *m/e* 343 (M^+) and 272 (retro-Diels–Alder), in agreement with the above findings. There were again characteristic peaks at *m/e* 178, 177, and 176.

The aglucone from *O*-methylalangiside, obtained in a similar manner, showed M^+ 357, $\lambda_{max.}$ 232 and 285 nm, and $\nu_{max.}$ 3 300 and 1 650 cm^{-1}. The mass spectrum showed the peaks corresponding to *m/e* 178 and 177 at *m/e* 192 and 191, respectively. The structural information obtained so far can be summarised in the partial formula (10).

† In view of recent work (C. Szántay, E. Szentirmay, and L. Szabo, *Tetrahedron Letters*, 1974, 3725), the structures of ankorine and alangimarckine may need to be revised with OH at position 8 instead of 11.

[1] Preliminary report, R. S. Kapil, A. Shoeb, S. P. Popli, A. R. Burnett, G. D. Knowles, and A. R. Battersby, *Chem. Comm.*, 1971, 904.

[2] A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, *Tetrahedron Letters*, 1966, 4965.

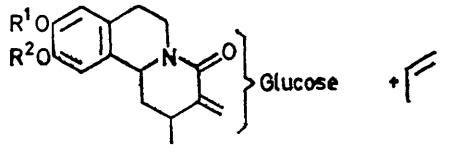
[3] S. C. Pakrashi and B. Achari, *Experientia*, 1970, **26**, 933 and references therein.

[4] S. P. Popli, Symposium on Chemistry of Natural Products, at Tashkent, Uzbek (U.S.S.R.), Sept. 16—20, 1968, Abstracts (supplement), p. 24.

[5] P. Bellet, *Ann. pharm. franç.*, 1952, **10**, 81.

[6] A. R. Battersby, B. Gregory, H. Spencer, J. C. Turner, M.-M. Janot, P. Potier, P. Francois, and J. Levisalles, *Chem. Comm.*, 1967, 219.

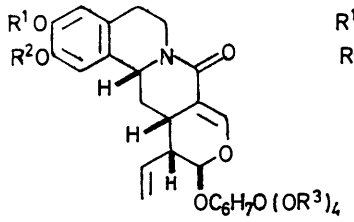
Treatment of alangiside with pyridine–acetic anhydride gave a penta-acetate (13), M^+ 715, $\nu_{max.}$ 1 750 cm^{-1}. The n.m.r. spectrum showed signals for the five

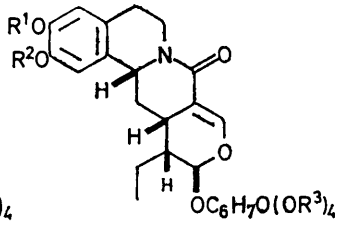


(10)
R^1=H,R^2=Me
or R^1=Me,R^2=H

acetoxy-groups as well as two separate signals for the aromatic protons. In the mass spectrum, new peaks appeared at *m/e* 386, 368, and **331** (base peak). Catalytic hydrogenation of (13) furnished the dihydroalangiside penta-acetate (14).

Treatment of alangiside with diazomethane afforded *O*-methylalangiside (15) M^+ 519, acetylation of which gave the corresponding tetra-acetate (16) M^+ 687.





(11) R^2=R^3=H,R^1=Me
(12) R^1=R^3=H,R^2=Me
(13) R^1 or R^2=R^3=Ac,R^2 or R^1=Me
(15) R^1=R^2=Me,R^3=H
(16) R^1=R^2=Me,R^3=Ac

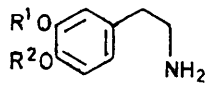
(14) R^1 or R^2=R^3=Ac, R^2 or R^1=Me

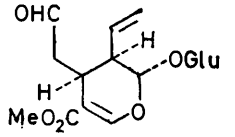
The foregoing data, in conjunction with biogenetic considerations, lead to structure (11) or (12) for alangiside.

Correlation with deacetylipecoside (6) was therefore attempted (in the laboratories of Professor Battersby):[1] methylation of the lactam obtained from deacetylipecoside with diazomethane gave the ether (15), identical (spectroscopy and chromatography) with *O*-methylalangiside. Thus structure (15) is a complete representation of *O*-methylalangiside and either of the two structures (11) or (12) is admissible for alangiside.

To distinguish between these structures, a synthesis of alangiside was undertaken. At this stage, we were informed of an abundant source of the valuable intermediate, secologanin,[7] from plants of the *Lonicera* species. The illustrated Scheme for the synthesis of the two isomers (11) and (12) was then devised.

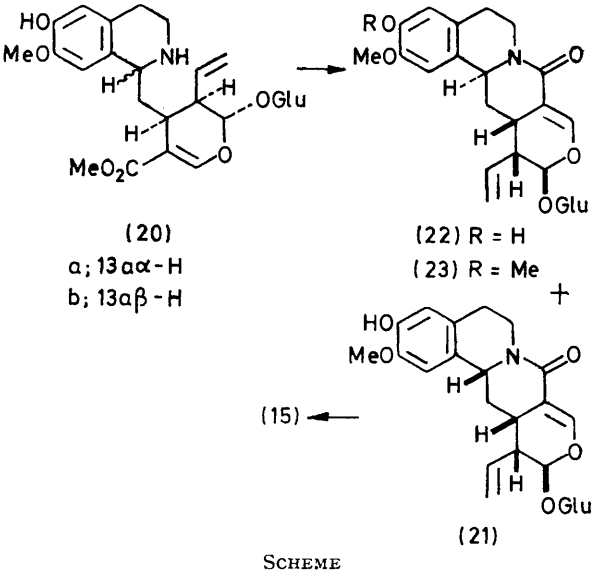
Attempted condensation of 4-hydroxy-3-methoxyphenethylamine (17) hydrochloride with secologanin (18) under a variety of conditions was not successful. However, 3-hydroxy-4-methoxyphenethylamine (19) condensed smoothly[8] with secologanin to give the stereoisomers (20a and b). No attempts were made to obtain the individual epimers in pure form and the crude mixture was treated with a 15% solution of sodium carbonate





(17) R^1=Me,R^2=H
(19) R^1=H,R^2=Me

(18)



(20)
a; 13aα-H
b; 13aβ-H

(22) R = H
(23) R = Me

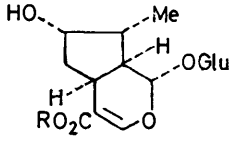
(15)

(21)

SCHEME

at room temperature for 30 min. The product consisted mainly of the β-epimer (21), which differed (optical rotation and n.m.r. spectrum) from alangiside and on treatment with diazomethane afforded a compound identical (spectra and t.l.c.) with naturally derived *O*-methylalangiside. This confirmed the stereochemistry of the synthetic product as well as the location of the phenolic hydroxy-group in alangiside (11).

If the reaction mixture was left for a longer time, besides the 13aβ-isomer (21), the 13aα-isomer (22) could also be isolated; this was characterised as its *O*-methyl-ether (23).



(24) R = Me
(25) R = H

In view of the importance of loganin (24) as an established precursor in the biosynthesis of the *Ipecacuanha*

[7] Personal communications from C. R. Hutchinson and A. R. Battersby; *cf.* I. Souzu and H. Mitsuhashi, *Tetrahedron Letters*, 1970, 191.

[8] A. R. Battersby, A. R. Burnett, and P. G. Parsons, *J. Chem. Soc.* (*C*), 1969, 1187.

[9] A. R. Battersby and B. Gregory, *Chem. Comm.*, 1968, 134; A. R. Battersby and R. J. Parry, *ibid.*, 1971, 901.

alkaloids [9] as well as the bearing it has on the structure of alangiside, a search for this intermediate was also made in various parts of the plant collected in different seasons. Loganic acid (25) was isolated in 0·2% yield from the fresh unripe fruit of *A. lamarckii*.

EXPERIMENTAL

Isolation of Alangiside (11).—The pulverised fruits (3·0 kg) of *A. lamarckii* collected locally were percolated with ethanol (10 × 1·5 l), the extract was evaporated below 40° in *vacuo*, and the residue was diluted with water (500 ml). The solution was filtered, defatted with light petroleum ether, adjusted to pH 10 (Na_2CO_3), and extracted with ether–chloroform (4 : 1; 4 × 625 ml) to remove basic material. The aqueous layer was saturated with NaCl (60 g), brought to pH 4 (concentrated HCl), and extracted with chloroform–ethanol (4 : 1; 4 × 625 ml). The combined organic extract was washed with brine (50 ml), dried (Na_2SO_4), and concentrated to afford a residue (5·60 g), which was subjected to counter-current distribution (Bu^nOH–EtOAc–H_2O, 3 : 2 : 5; 10 ml fractions; 100 transfers). The contents of the tubes 55—69 were mixed on the basis of u.v. and n.m.r. data and afforded a cream-coloured powder which was further purified by column chromatography (silica gel; EtOAc–EtOH, 98 : 2) to furnish *alangiside* (2·25 g) as a white amorphous powder shrinking at 164° and melting at 187° (decomp.), $[\alpha]_D^{26}$ −105° (*c* 1·0 in MeOH) $\nu_{max.}$ (KBr) 3 350br (OH), 1 650 (=N–C=O), 1 585, 1 510, 1 450, 1 440, 1 020, and 910 cm^{-1}, τ [$(CD_3)_2SO$: 60 MHz] 2·61(1H, d, *J* 1·5 Hz, O–CH=), 3·25 (2H, s, ArH), 4·60 (3H, m, $CH{=}CH_2$), and 6·21 (3H, s, OMe), *m/e* 505 (M^+), 343, 274 (base), 272, 178, 177, and 176 (Found: C, 54·25; H, 6·55; N, 2·3%; M^+, 505·1925. $C_{25}H_{31}NO_{10},2{\cdot}5H_2O$ requires C, 54·55; H, 6·55; N, 2·55%. $C_{25}H_{31}NO_{10}$ requires *M*, 505·1947).

Alangiside Penta-acetate (13).—A mixture of alangiside (500 mg), acetic anhydride (10·0 ml), and pyridine (5·0 ml) was kept overnight at room temperature. Solvents were removed under reduced pressure and the residue was diluted with water and extracted with benzene (3 × 10 ml). The extracts were combined, washed with water, dried (Na_2SO_4), and evaporated to afford the *penta-acetate* (13) (400 mg), which was further purified over a column of silica gel; $\nu_{max.}$ ($CHCl_3$) 1 750 (OAc) and 1 655 cm^{-1} (=N–C=O), τ ($CDCl_3$) 2·54 (1H, d, *J* 2·5 Hz, O–CH=), 3·14 and 3·27 (1H each, both s, ArH), 5·75 (2H, m, CH_2·OAc), 6·18 (3H, s, OCH_3), 7·70 (3H, s, phenolic OAc), and 7·90, 7·97, 8·00, and 8·04 (3H each, all s, 4 OAc), *m/e* 715 (M^+), 673, 386, 384, 368, 331 (base), 316, 220, 178, 177, 176, 170, 169, 127, and 109 (Found: C, 57·1; H, 5·95; N, 1·75%; M^+, 715·2446. $C_{35}H_{41}NO_{15},H_2O$ requires C, 57·3; H, 5·85; N, 1·9%. $C_{35}H_{41}NO_{15}$ requires *M*, 715·2475).

Dihydroalangiside Penta-acetate (14).—A solution of the penta-acetate (13) (60 mg) in ethanol (25 ml) was stirred with Adams catalyst (30 mg) for 2 h in hydrogen. Filtration and concentration under reduced pressure afforded the *dihydro-derivative* (14) (58 mg), $[\alpha]_D^{26}$ −120° (*c* 1·0 in MeOH), $\nu_{max.}$ (KBr) 1 750 and 1 655 cm^{-1}, τ ($CDCl_3$) 2·55 (1H, d, O–CH=), 3·08 and 3·22 (1H each, s, ArH), 5·74 (2H, m CH_2·OAc), 6·15 (3H, s, OMe), 7·89, 7·95, 7·99, and 8·02 (1 phenolic OAc, 4 alcoholic OAc), and 9·01 (3H, t, CH_2Me), *m/e* 717 (M^+), 675, 430, 371, 370, 369, 331, 298, 274, 272, 229, 178, 177, and 169 (Found: M^+, 717·2568. $C_{35}H_{43}NO_{15}$ requires *M*, 717·2632).

O-*Methylalangiside* (15).—A solution of alangiside (150 mg) in the minimum quantity of methanol was treated with ethereal diazomethane [from *N*-nitrosomethylurea (350 mg)] and set aside overnight at room temperature. The solvent was removed and the residue (140 mg) was chromatographed over a column of silica gel to afford the O-*methyl derivative* (15) (70 mg), obtained as needles (from EtOAc), m.p. 236°, $\nu_{max.}$ (KBr) 3 375 and 1 655 cm^{-1}, τ ($CDCl_3$) 2·42 (1H, s, OCH=), 3·20 and 3·35 (1H each, s, ArH), 4·60 (3H, m, olefinic H), and 6·10 and 6·14 (each 3H, s, OMe), *m/e* 519 (M^+), 505, 358, 357, 356, 340, 288 (base), 274, 272, 270, 258, 257, 256, 192, 191, 178, 177, 176, 149, and 145 (Found: C, 56·85; H, 6·85; N, 2·35%; M^+, 519·2080. $C_{26}H_{33}NO_{10},1{\cdot}5H_2O$ requires C, 57·15; H, 6·6; N, 2·55%. $C_{26}H_{33}NO_{10}$ requires *M*, 519·2104).

O-*Methylalangiside Tetra-acetate* (16).—A solution of O-methyl alangiside (15) (150 mg) in acetic anhydride (6 ml) and pyridine (3 ml) was left overnight at room temperature. The excess of reagent was removed under reduced pressure and the residue was diluted with water and extracted with benzene (3 × 15 ml). The extract was washed with water, dried (Na_2SO_4), and concentrated. The residue (120 mg) was chromatographed on a column of silica gel to furnish the *tetra-acetate* (16), $\nu_{max.}$ (KBr) 1 750 and 1 655 cm^{-1}, τ ($CDCl_3$) 2·49 (1H, d, OCH=), 3·34br (2H, s, ArH), 5·72 (2H, m, CH_2·OAc), 6·10 (6H, s, 2 OCH_3), and 7·89, 7·95, 7·99, and 8·00 (each 3H, s, 4 OAc), *m/e* 687 (M^+), 400, 399, 356, 340, 331, 330, 288, 192, 191, 177, 169, 149, 145, 139, 127, 109, and 97 (Found: M^+, 687·2502. $C_{34}H_{41}NO_{14}$ requires *M*, 687·2526).

Hydrolysis of Alangiside.—A suspension of alangiside (50 mg) and β-glucosidase (100 mg) in water (5 ml) and toluene (2 drops) was kept at room temperature for 3 days. It was then diluted with ethanol–chloroform (2 : 1 : 150 ml) and filtered. The filtrate was concentrated and the residue repeatedly extracted with chloroform (8 × 10 ml). Removal of the solvent afforded the *aglucone* (10 mg) as a white amorphous powder giving a single spot on t.l.c. (silica gel; EtOAc); $\nu_{max.}$ (KBr) 3 350br (OH), 1 655 cm^{-1} (=N–C=O), *m/e* 343 (M^+), 325, 314, 272, 243, 178, 177, and 176 (Found: M^+, 343·1435. $C_{19}H_{21}NO_5$ requires *M*, 343·1419).

Hydrolysis of O-*Methylalangiside.*—By the procedure described above the corresponding *aglucone* was obtained as a light yellow amorphous powder, which when passed through a silica gel column yielded the pure product (t.l.c. on silica gel: EtOAc); $\nu_{max.}$ (KBr) 3 300br (OH) and 1 650 cm^{-1} (=N–C=O), *m/e* 357 (M^+), 342, 339, 328, 286, 272, 244, 242, 192, 191, 190, 177, and 176 (Found: M^+, 357·1558. $C_{20}H_{23}NO_5$ requires *M*, 357·1576).

3-O-*Demethyl*-2-O-*methylalangiside* (21).—A mixture of 3-hydroxy-4-methoxyphenethylamine (19) hydrochloride (125 mg) and secologanin (18) (250 mg) in phosphate buffer (pH 5·2; 4·5 ml) was kept for 4 days at 37° under oxygen-free nitrogen. The reaction was monitored by t.l.c. The mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 × 10 ml). The aqueous layer was further stirred at room temperature with aqueous 15% sodium carbonate (3 ml) for 30 min, then re-extracted with ethyl acetate, followed after 2·5 h by n-butanol (4 × 10 ml).

The ethyl acetate layer was concentrated and the residue (100 mg) chromatographed on a column of silica gel (5·0 g). Elution with 10% methanol–chloroform gave an amorphous *powder* (21), $[\alpha]_D^{25}$ −82·9° (*c* 0·85 in MeOH), $\nu_{max.}$ (KBr) 3 350 and 1 650 cm^{-1}, τ [$(CD_3)_2SO$] 2·73 (1H, d, *J* 2·0 Hz, O–CH=), 3·20 (1H, s, ArH), 3·49 (1H, s, ArH), 4·60 (3H, m, $CH{=}CH_2$), and 6·25 (3H, s, OMe) (Found: M^+, 505·1964. $C_{25}H_{31}NO_{10}$ requires *M*, 505·1947).

The n-butanol fraction on concentration gave a residue (200 mg) which was chromatographed on a column of silica gel (10·0 g). Elution with 10% methanol–chloroform afforded a powder (150 mg) [single spot on t.l.c. (silica gel; 20% MeOH in $CHCl_3$)]. Its n.m.r. spectrum indicated it to be a mixture of two components. The major one (65%) appeared to be (21) and the minor one (35%) was characterised as 3-O-*demethyl*-2-O-*methylisoalangiside* (22), τ [$(CD_3)_2$-SO] 2·80 (1H, d, *J* 2·0 Hz, O–CH=), 3·20 (1H, s, ArH), 3·49 (1H, s, ArH), 4·60 (3H, m, $CH{=}CH_2$), and 6·25 (3H, s, OMe) (Found: M^+, 505·1978).

O-*Methylisoalangiside* (23).—A mixture of compounds (21) and (22) obtained from the foregoing n-butanol fraction was treated with an excess of diazomethane. Column chromatography on silica gel (15·0 g) afforded a fraction largely consisting of compound (23), τ [$(CD_3)_2SO$] 2·74 (1H, d, *J* 2·0 Hz, OCH=), 3·10 (1H, s, ArH), 3·21 (1H, s, Ar*H*), 4·60 (3H, m, $CH{=}CH_2$), and 6·21 (6H, s, 2 OMe) (Found: M^+, 519·2120. $C_{26}H_{33}NO_{10}$ requires *M*, 519·2104). The later fractions from the column yielded *O*-methylalangiside (15) (100 mg), m.p. 236°.

Isolation of Loganic Acid (25).—The n-butanol fraction (10 g) from the unripe green fruits (3·0 kg) of *A. lamarckii* was subjected to counter-current distribution (10 ml fractions; 100 transfers) in n-butanol–water (2 : 3). Tubes 26—36 afforded a fraction (850 mg) rich in (25). Part of the crude loganic acid (270 mg) was chromatographed on a column of silica gel (10 g); elution with ethyl acetate gave (25) (200 mg) as a pure white powder, $\lambda_{max.}$ (MeOH) 238 nm, $\lambda_{max.}$ (MeOH–0·1N-NaOH) 229 nm, $\nu_{max.}$ (KBr) 3 350br (OH), weak bands in the region 2 700—2 500, 1 675br (C:O), and 1 625 cm^{-1} (C:C), τ (D_2O) 2·50br (1H, C:CH·O), 4·60 (1H, d, *J* 3 Hz, *H*C·C·OGlu), and 8·88 (3H, d, *J* 7 Hz, CHMe).

Loganin (24)—A solution of loganic acid (25) (200 mg) in methanol (2 ml) was treated with diazomethane [from *N*-nitrosomethylurea (250 mg)] and chromatographed on a column of silica gel (EtOAc) to yield pure loganin (120 mg), m.p. 222—223°, $[\alpha]_D^{25}$ −83° (*c* 1·0 in H_2O), identical with an authentic sample [mixed m.p. t.l.c. (silica gel; 10% EtOH–$CHCl_3$), and i.r. spectrum: $\nu_{max.}$ (KBr) 3 500 (OH), 3 300 (OH), 1700 (CO_2Me), and 1 650 cm^{-1} (C=C)].

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