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DAPHNIPHYLLUM ALKALOIDS—III*

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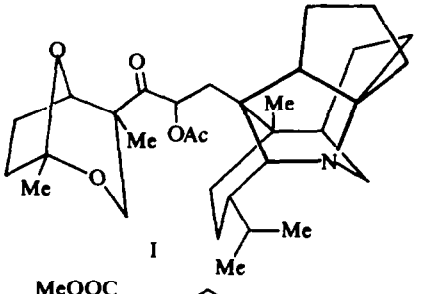
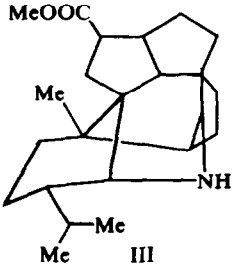
Abstract—The structures of yuzurimine and yuzurimines-A and B are presented. The structure of yuzurimine, established by X-ray analysis, is in full agreement with its chemical and spectral data. The structures of yuzurimines-A and B were deduced by comparison of the NMR, IR and mass spectra with those of yuzurimine. The structure of the latter was confirmed by chemical transformation from yuzurimine to yuzurimine-B mesylate. Finally, chemical transformation of yuzurimine to a biogenetically plausible compound (XXXI or XXXII) was carried out.

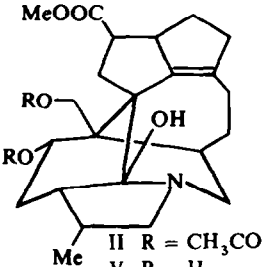
ALKALOIDS of *Daphniphyllum macropodum* Miquel have been examined and a number of new alkaloids[1] have been isolated. These proved to have very unusual carbon skeletons by X-ray diffraction studies [daphniphylline (I),[2,3] yuzurimine (II),[4] methyl homosecodaphniphyllate (III),[5,6] and daphnilactone-B (IV)†].



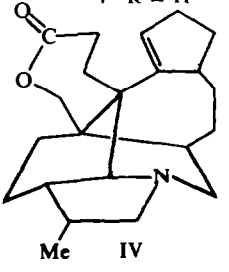
I



III



II R = CH_3CO
V R = H



IV

* Part II: See ref. 6.

† IV was isolated from the fruits of the same plant and the X-ray analysis of this free base was carried out by K. Sasaki.[7]

In the present paper, the structures and chemical properties of yuzurimine and yuzurimines-A and B are discussed.

Physical and chemical properties of yuzurimine (II). Physical and chemical data of yuzurimine are in full agreement with the structure II, as discussed below. The NMR spectrum of yuzurimine hydrochloride is shown in Fig 1, and its remarkable signals as well as their assignments are also described.

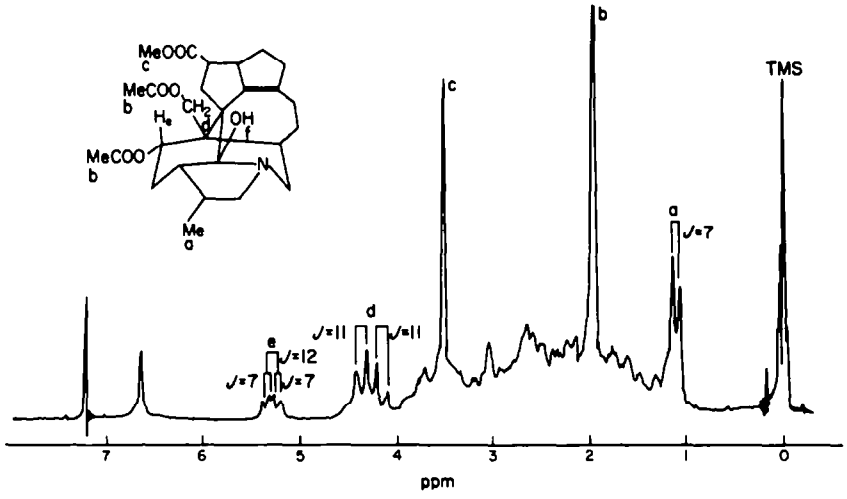
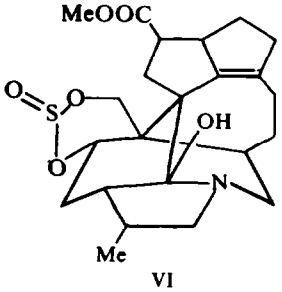
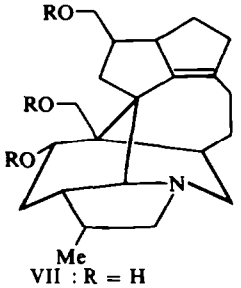


FIG 1. The NMR spectrum of yuzurimine hydrochloride

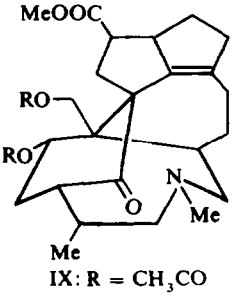
Hydrolysis of II with methanolic sodium hydroxide or 15% HCl-MeOH gave desacetyl yuzurimine V. Further treatment of V with thionyl chloride in pyridine did not give a dichloride nor a dehydration product, but instead a sulfite VI. The formation of VI indicates that both primary and secondary OH groups are sterically close to each other. Reduction of II with LAH in THF gave a triol VII which reacted with mesyl chloride in pyridine to give a trimesylate VIII. However, these three mesyloxyl groups seem to be sterically hindered, for LAH reduction of VIII affords only the original triol (VII). The presence of HO—C—N< group in yuzurimine can be chemically supported as follows. Yuzurimine methiodide, gave a keto-amine (IX) only



VI



VII : R = H
VIII: R = CH_3SO_2



IX: R = CH_3CO
X : R = H

by contact with aqueous alkaline solution. Furthermore, treatment of the methiodide with methanolic sodium hydroxide gave a desacetyl keto-amine (X). Extraordinary low CO frequencies, 1633 cm^{-1} in IX and 1600 cm^{-1} in X, seem to be due to close proximity of the N atom with a lone pair of electrons.[8] The sterically hindered CO group of IX was not reduced by sodium borohydride in THF (under reflux for 21 hr). The above chemical experiments are fully consistent with the structure II.

Structure of yuzurimine-A. Yuzurimine-A, a minor alkaloid, has a molecular formula $C_{25}H_{35}O_5N{\cdot}HCl$ as hydrochloride. Its IR spectrum is very similar to that of yuzurimine hydrochloride. On the basis of careful comparison of the NMR spectra of yuzurimine hydrochloride (Fig 1) and yuzurimine-A hydrochloride, shown in Fig 2, coupled with the difference of mass number ($C_2H_2O_2$ = 58) between them, the structure of the latter can be deduced, as discussed below.

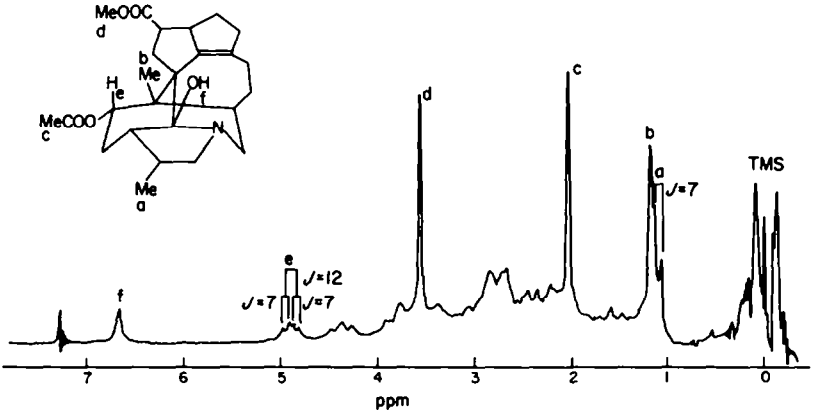
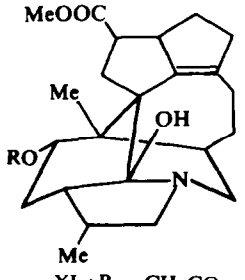


FIG 2. The NMR spectrum of yuzurimine-A hydrochloride

The signals at 1·98 ppm (6H, s) and the AB quartet centered at 4·32 ppm (2H, q, J = 11 Hz), which can be assigned to acetoxyl and acetoxy-methyl groups respectively, are observed in the NMR spectrum of yuzurimine hydrochloride (II). On the other hand, yuzurimine-A hydrochloride has a tertiary Me signal at 1·17 ppm instead of the acetoxy-methyl signals in II. The remaining signals are nearly identical in both compounds. Therefore, yuzurimine-A can be regarded as desacetoxy-yuzurimine (XI). Finally, hydrolysis of yuzurimine-A with 10% HCl–MeOH afforded desacetyl yuzurimine-A (macrodaphniphyllamine) [XII; m.p. 251–254° (as hydrochloride);



XI ; R = CH_3CO
XII: R = H

$C_{23}H_{33}O_4N{\cdot}HCl$; ν_{max}(nujol) 3370, 3140 and 1724 cm^{-1}], which had been isolated by Nakano *et al.*[9]

Structure of yuzurimine-B. The structure of the other minor alkaloid, yuzurimine-B can also be estimated by comparison of its spectral data (NMR, IR and mass spectra) with those of yuzurimine.[9] The NMR spectrum of yuzurimine-B hydrochloride in deuterium oxide is shown in Fig 3. The NMR signals at 1·22 (3H, d, J = 6 Hz) and

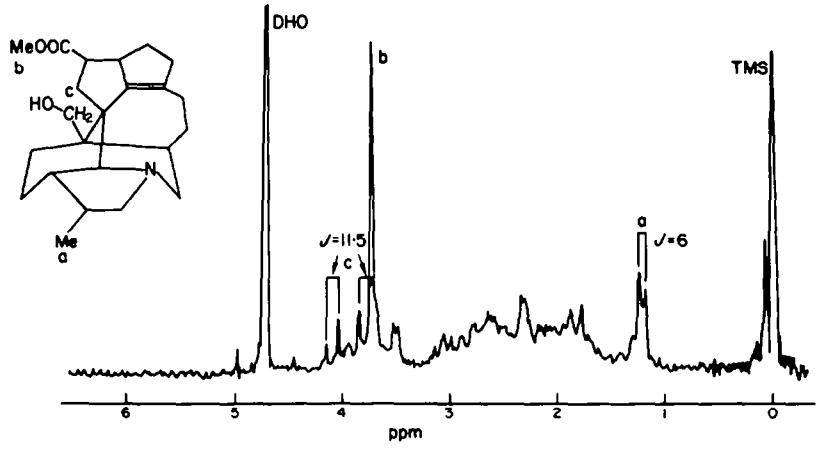
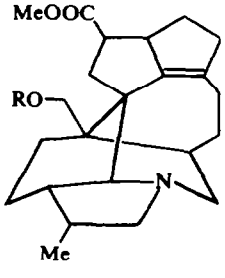
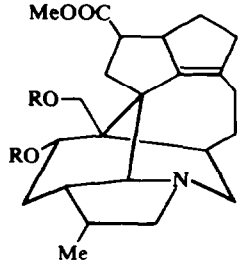


FIG 3. The NMR spectrum of yuzurimine-B hydrochloride

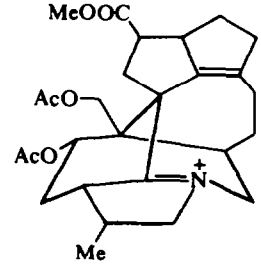
3·72 (3H, s) ppm are due to secondary Me and carbomethoxy groups respectively. Furthermore, the AB quartet centered at 3·94 (2H, q, J = 11·5 Hz) ppm indicates the presence of a tertiary hydroxymethyl group. This fact was supported by acetylation of yuzurimine-B hydrochloride, which afforded yuzurimine-B acetate (macrodaphniphyllidine XIII). XIII had also been isolated by Nakano *et al.*[9] In its NMR spectrum, the new signals at 2·08 (3H, s) and 4·47 (2H, s) ppm are observed instead of the AB quartet at 3·94 ppm in yuzurimine-B hydrochloride. Therefore, comparison of the NMR spectra between yuzurimine hydrochloride and yuzurimine-B hydrochloride (Figs 1 and 3), coupled with the difference of molecular weight ($C_4H_4O_4$ = 116) and absence of the acetoxyl group in the latter, suggests the structure XIV for yuzurimine-B. Finally, this conclusion was confirmed by chemical transformation from yuzurimine (II) to yuzurimine-B mesylate (XV), as described below.



XIII: R = CH_3CO
XIV: R = H
XV: R = CH_3SO_2

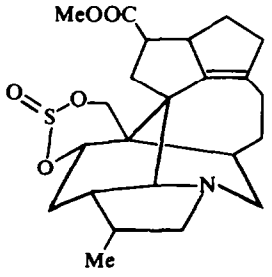


XVI: R = CH_3CO
XVIII: R = H
XX: R = CH_3SO_2

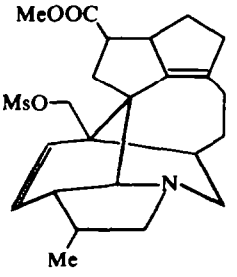


XVII

Reduction of yuzurimine (II) with active zinc powder in glacial acetic acid (90–95°, for 2 hr) gave desoxy-yuzurimine (XVI). In the course of reduction, the reduction intermediate seems to be an imino-compound (XVII).* Further treatment of XVI with 7% HCl–MeOH gave desacetyl desoxy-yuzurimine (XVIII), which was also prepared from desacetyl yuzurimine (V) by reduction with active zinc powder in glacial acetic acid. To remove the secondary OH group in XVIII, attempted dehydration with thionyl chloride in pyridine has been failed: XVIII reacted with thionyl chloride in dimethyl formamide to give only a sulfite (XIX). However, when treated with mesyl chloride in pyridine, XVIII gave a dimesylate (XX). Furthermore, XX was treated with lithium chloride in dimethyl formamide at 90–100° for 18 hr. to give a monomesylate (XXI). In the NMR spectrum of XXI, a new singlet at 5·93 (2H)



XIX



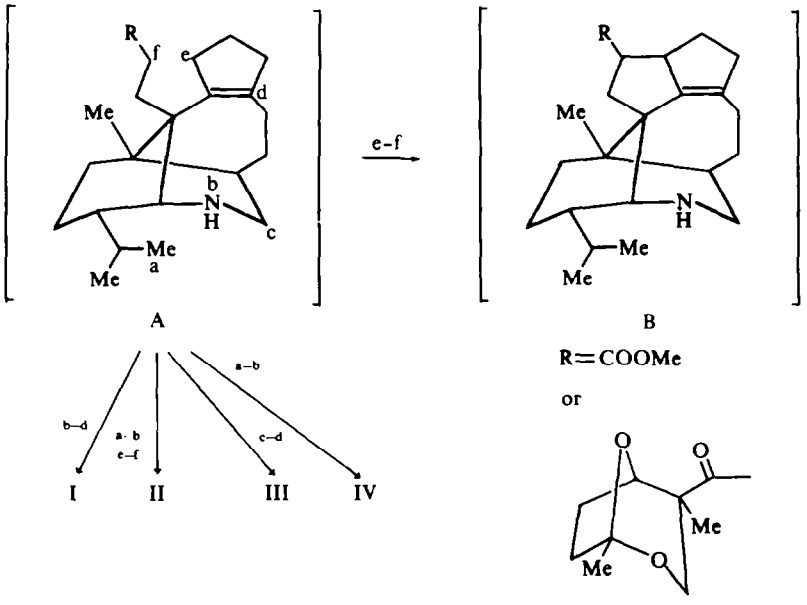
XXI

ppm appeared instead of a quartet centered at 5·16 (1H) ppm in XX, showing the presence of a disubstituted double bond. Catalytic hydrogenation of XXI over PtO_2 gave a reduction product (XV). There is no olefinic proton signal in the NMR spectrum of XV. When treated with mesyl chloride in pyridine, yuzurimine-B hydrochloride (XIV) gave a monomesylate, which was completely identical with XV obtained from yuzurimine (II) (mixed m.p. and IR spectrum). Therefore, the structure of yuzurimine-B can be represented by XIV.

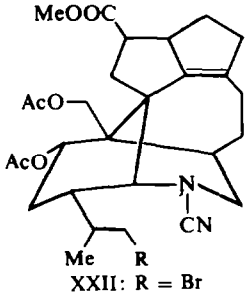
Structural relationship among daphniphyllum alkaloids. X-ray diffraction revealed the unusual structures of four daphniphyllum alkaloids, which had different carbon skeletons but were formally related to one another by bond formation, bond fission and so on. As shown below, a plausible compound (A), which has not yet been isolated, is regarded as a common intermediate among these alkaloids. Such a compound as (B) also has not yet been isolated from the plant, but was chemically transformed from yuzurimine (II) as follows.

Von Braun degradation of desoxy-yuzurimine (XVI) with cyanogen bromide in benzene gave a bromo-cyanamide (XXII or XXIII), which was reduced with sodium borohydride in dimethyl sulfoxide[11] to give a cyanamide (XXIV or XXV). In the NMR spectrum of XXII (or XXIII), there is one secondary Me signal at 1·18 (3H, d, $J = 5$ Hz) ppm. On the other hand, two secondary Me signals at 0·99 (3H, d, $J = 5$ Hz) and 1·05 (3H, d, $J = 5$ Hz) ppm are observed in the NMR spectrum of XXIV (or XXV). However, in the case of Von Braun degradation of XVI, two possible products are considered (XXII or XXIII for the bromo-cyanamide and XXIV or XXV for the cyanamide). To determine the position of the Br atom, dehydrobromination of XXII

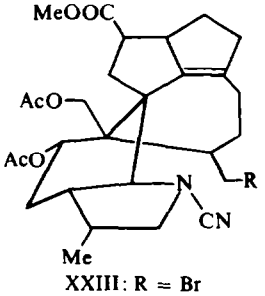
* XVII has a 2-azabicyclo[3.3.1] non-1-ene system. Such an anti-Bredts' rule imine has been obtained by oxidation of methyl homosecodaphniphyllate (III) with lead tetra-acetate.[10]



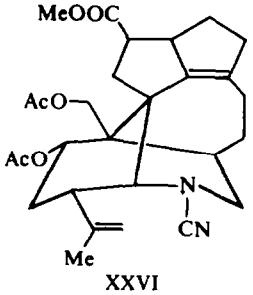
(or XXIII) with silver fluoride in pyridine was carried out at room temperature for 4 days to give an olefine [XXVI; m.p. 186–188°; ν_{max}(KBr) 2200 and 1645 cm^{-1}]. In its NMR spectrum, a singlet at 1·89 (3H) ppm appeared instead of a doublet at 1·18 (3H, d, J = 5 Hz) ppm in the bromo-cyanamide. This fact indicates the structure XXII for the bromo-cyanamide and XXIV for the cyanamide. Catalytic hydrogenation of XXVI over PtO_2 gave XXIV, as can be expected.



XXII: R = Br
XXIV: R = H

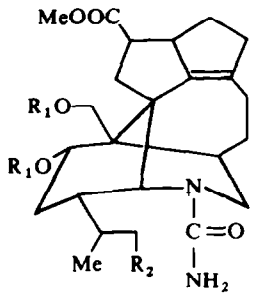


XXIII: R = Br
XXV: R = H

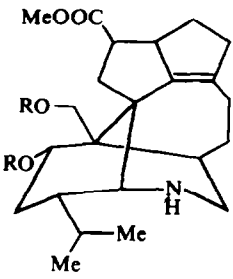


XXVI

Hydrolyses of XXII and XXIV with 17% HCl–MeOH gave a desacetyl bromo-urea (XXVII) and a desacetyl urea (XXVIII), respectively. When treated with glacial acetic acid under reflux for 22 hr, XXII gave desoxy-yuzurimine (XVI) and a bromo-urea (XXIX) in 65 and 7% yields, respectively. XXIV was treated with acetic acid saturated with hydrogen chloride under reflex for 46 hr to give a urea (XXX) and a secondary amine (XXXI) in 19 and 49% yields, respectively. The amine (XXXI) was further hydrolysed with methanolic sodium hydroxide to afford a compound (XXXII).



XXVII: $R_1 = H, R_2 = Br$
XXVIII: $R_1 = R_2 = H$
XXIX: $R_1 = CH_3CO, R_2 = Br$
XXX: $R_1 = CH_3CO, R_2 = H$



XXXI : R = CH_3CO
XXXII: R = H

The above compounds (XXXI and XXXII) seem to be one of the biogenetic intermediates of daphniphyllum alkaloids. Studies are now in progress to isolate minor components.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra were recorded with a Hitachi Grating Infrared Spectrophotometer EPI-G3 or a JASCO Model IR-S. The UV spectra were measured in EtOH soln with a Beckman DK-2 Spectrometer. The NMR spectra were obtained on a Varian Associates AH-100 or a JNMC-60H. Chemical shifts for all NMR spectra are given in ppm from TMS as internal standard using $CDCl_3$ as solvent. Only prominent peaks are cited (d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet). The mass spectra were recorded with a Hitachi RMU-6D mass spectrometer with an ionization energy of 70 eV.

Physical properties of yuzurimine, yuzurimines-A and B. Isolation of yuzurimine, yuzurimines-A and B has been reported in the previous paper.[3,6] Physical data of these three alkaloids are described below.

Yuzurimine (II), m.p. 150–152° (from acetone); ν_{max}(nujol) 3490, 1744, 1735, 1722, 1264 and 1040 cm^{-1}: m.p. 251–253° (as hydrobromide, in a sealed tube, from MeOH); ν_{max}(KBr) 3440, 2940, 1733 and 1246 cm^{-1}. (Found: C, 57·23; H, 6·76; N, 2·87. $C_{27}H_{37}O_7N$·HBr requires: C, 57·04; H, 6·74; N, 2·46%). This hydrobromide was used for X-ray analysis.[4]

Yuzurimine-A (XI), m.p. 249–252° (dec) (as hydrochloride, in a sealed tube, from MeOH-ether); ν_{max}(KBr) 3430, 2600(br), 1732(br), 1240, 1164 and 1030 cm^{-1}; ν_{max}(nujol) 3170, 1732, 1248, 1165 and 1034 cm^{-1}; $\lambda_{210\,nm}$ 6250 (end absorption); *m/e* 429 (24, M^+-HCl), 411 (65), 370 (11), 368 (14) and 352 (100). (Found: C, 64·89; H, 7·82; N, 3·20. $C_{25}H_{35}O_5N$·HCl requires: C, 64·43; H, 7·79; N, 3·01%).

Yuzurimine-B (XIV); m.p. 282–284·5° (as hydrochloride, in a sealed tube, from MeOH); ν_{max}(KBr) 3440, 2600(br), 1735, 1167 and 1028 cm^{-1}; ν_{max}(nujol) 3280, 1736, 1270, 1170 and 1034 cm^{-1}; $\lambda_{210\,nm}$ 7230 (end absorption); *m/e* 371 (57, M^+-HCl), 354 (14), 340 (39) and 312 (9). (Found: C, 67·76; H, 8·34; N, 3·56. $C_{23}H_{33}O_3N$·HCl requires: C, 67·70; H, 8·40; N, 3·43%).

Desacetyl yuzurimine (V)

(a). To a soln of yuzurimine (323 mg) in abs MeOH (4 ml) was added NaOH (160 mg) in abs MeOH (3 ml). The soln was allowed to stand at room temp overnight and then diluted with water, and extracted with $CHCl_3$. The extracts were washed well with water and dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from $CHCl_3$-ether to afford white crystals of V (235 mg, 88%). Recrystallization from $CHCl_3$-ether gave colourless needles; m.p. 174–176°; ν_{max}(nujol) 3350, 1743, 1164 and 1035 cm^{-1}; δ 1·08 (3H, d, J = 7 Hz) and 3·67 (3H, s) ppm; *m/e* 403 (36, M^+), 385 (61), 372 (15), 354 (59), 326 (100) and 296 (64). (Found: C, 68·26; H, 8·07; N, 3·57. $C_{23}H_{33}O_5N$ requires: C, 68·46; H, 8·24; N, 3·47%).

(b). A soln of yuzurimine (3·545 g) in 15% HCl–MeOH (50 ml) was refluxed for 20 hr. After cooling, the soln was concentrated under reduced press to give crystals of V (as hydrochloride), which was collected by filtration. Further concentration of the filtrates gave an oil, which was crystallized from MeOH-ether to

afford crystals of V. These two fractions (3·089 g, 96%) were combined together and recrystallized from MeOH-ether to give colourless plates; m.p. 217–220° (as hydrochloride); ν_{max}(nujol) 3490, 3430, 3300, 1727, and 1032 cm^{-1}. A suspension of a small amount of the above crystals in $CHCl_3$ was shaken with aqueous NaOH, and then the organic layer was washed with water and dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was recrystallized from $CHCl_3$-ether to afford the same colourless needles as V, which had been obtained by the method (a) (m.p. and IR spectrum).

Formation of the sulfite (VI). Thionyl chloride (0·3 ml) was added to a soln of desacetyl yuzurimine (132 mg) in dry pyridine (2 ml) cooled in an ice-bath. The soln was allowed to stand at 0° for 1 hr and at room temp for 4 hr, and then poured into water. The aqueous soln was made basic (pH > 10) with 10% NaOH aq, and extracted with benzene. The extracts were washed with water and sat NaCl aq, and then dried over Na_2SO_4. The solvent was removed under reduced press to give slightly coloured crystals, which were washed with acetone (1 ml) and recrystallized from $CHCl_3$-ether to afford colourless needles of VI (47 mg, 32%); m.p. 237–239°; ν_{max}(nujol) 3430, 1730, 1160, 945, 924, 839 and 770 cm^{-1}; δ 1·05 (3H, d, J = 7 Hz), 3·65 (3H, s), 4·22 (1H, d, J = 13 Hz), 5·25 (1H, q, J = 10 and 8 Hz) and 5·36 (1H, d, J = 13 Hz) ppm; *m/e* 449 (100, M^+), 431 (78), 400 (18) and 372 (22) (Found: C, 60·91; H, 6·78; N, 2·92. $C_{23}H_{31}O_6NS$ requires: C, 61·44; H, 6·95; N, 3·11%).

Lithium aluminium hydride reduction of yuzurimine (II). To a soln of yuzurimine (667 mg) in THF (15 ml) was added LAH (276 mg). The mixture was refluxed for 5 hr with stirring. After excess LAH was decomposed with EtOAc, the soln was diluted with aqueous potassium sodium tartarate, and then extracted with $CHCl_3$. The extracts were washed with NaOH aq and dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from MeOH-ether to afford white crystals of VII (418 mg, 85%). Recrystallization from MeOH-ether gave colourless plates; m.p. 205–208°; ν_{max}(nujol) 3370 and 1022 cm^{-1}; *m/e* 359 (100, M^+), 342 (38), and 328 (53). (Found: C, 73·61; H, 9·31; N, 3·69. $C_{22}H_{33}O_3N$ requires: C, 73·50; H, 9·25; N, 3·90%).

Reaction of the triol (VII) *with mesyl chloride.* Mesyl chloride (0·5 ml) was added to a soln of VII (202 mg) in dry pyridine (2·5 ml) cooled in an ice-bath. The soln was stirred at 0° for 30 min and at room temp for 5 hr, and then poured into water. The aqueous soln was made basic (pH > 10) with 20% NaOH aq, and extracted with $CHCl_3$. The extracts were washed with water and dried over Na_2SO_4, and then concentrated under reduced press to give an oil, which was crystallized from EtOH to afford slightly coloured crystals of VIII (245 mg, 73%). Recrystallization from EtOH gave colourless needles; m.p. 172–173°; ν_{max}(nujol) 1365, 1355, 1338, 1173, 963 and 926 cm^{-1}; δ 1·12 (3H, d, J = 6 Hz), 3·03 (3H, s), 3·11 (3H, s), 3·18 (3H, s), 3·7–4·7 (4H, m) and 5·25 (1H, m) ppm. (Found: C, 50·45; H, 6·81; N, 2·17. $C_{25}H_{39}O_9NS_3$ requires: C, 50·57; H, 6·62; N, 2·36%).

Lithium aluminium hydride reduction of the trimesylate (VIII). To a soln of VIII (112 mg) in THF (10 ml) was added LAH (92 mg). The mixture was refluxed for 5 hr with stirring. After excess LAH was decomposed with EtOH, the soln was concentrated to *ca* 5 ml and diluted with aqueous potassium sodium tartarate, and then extracted with $CHCl_3$. The extracts were washed with NaOH aq, and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from MeOH-ether to afford colourless crystals of VII (28 mg, 38%) (m.p. and IR spectrum).

Yuzurimine methiodide. To a soln of yuzurimine (2·027 g) in acetone (50 ml) was added MeI (2 ml). The soln was refluxed for 6 hr. After cooling, the soln was concentrated under reduced press to give white crystals of the metiodide (2·583 g, 99%). Recrystallization from acetone gave colourless plates; m.p. 180–182°; ν_{max}(nujol) 3130, 1733, 1266, 1192, 1171 and 1047 cm^{-1}; δ 1·12 (3H, br. d, J = 5 Hz), 2·05 (3H, s), 2·07 (3H, s), 3·31 (3H, s), 3·66 (3H, s), 4·32 (2H, br. s), 5·40 (1H, m) and 6·31 (1H, br. s) ppm. (Found: C, 53·11; H, 6·39; N, 2·26. $C_{28}H_{40}O_7NI$ requires: C, 53·41; H, 6·41; N, 2·22%).

Formation of the keto-amine (IX). A soln of yuzurimine methiodide (1·209 g) in $CHCl_3$ (50 ml) was successively washed with NaOH aq and water, and then dried over Na_2SO_4. The organic layer was concentrated under reduced press to give an oil, which was crystallized from ether to afford white crystals of IX (773 mg, 80%). Recrystallization from isopropyl ether gave colourless plates; m.p. 136–138°; ν_{max}(CCl_4) 1745, 1633, 1244, 1196, 1172 and 1035 cm^{-1}; δ 0·83 (3H, d, J = J Hz), 2·00 (9H, s), 3·59 (3H, s), 4·28 (2H, s) znd 5·44 (1H, q, J = 12 and 7 Hz) ppm; *m/e* 501 (71, M^+), 486 (2), 470 (8), 442 (43) and 428 (10). (Found: C, 67·15; H, 7·88; N, 2·81. $C_{28}H_{39}O_7N$ requires: C, 67·04; H, 7·84; N, 2·79%).

Formation of the desacetyl keto-amine (X). To a soln of yuzurimine methiode (526 mg) in abs MeOH (5 ml) was added NaOH (207 mg) in abs MeOH (5 ml). The soln was allowed to stand at room temp overnight, and then diluted with water and extracted with $CHCl_3$. The extracts were washed with water, and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was

crystallized from acetone to afford white crystals of X (280 mg, 80%). Recrystallization from acetone gave colourless plates; m.p. 208–209°; ν_{max}(CHCl$_3$) 3600, 3460, 1722, 1600, 1168 and 1034 cm^{-1}; δ 0·88 (3H, d, J = 7 Hz), 2·12 (3H, s) and 3·63 (3H, s) ppm; *m/e* 417 (57, M$^+$), 386 (100) and 358 (18). (Found: C, 69·35; H, 8·94; N, 3·32. $C_{24}H_{35}O_5N$ requires: C, 69·03; H, 8·45; N, 3·35%).

Sodium borohydride reduction of the keto-amine (IX). A mixture of IX (80 mg) and $NaBH_4$ (180 mg) in THF (10 ml) was refluxed for 21 hr with stirring. After cooling, the reaction soln was diluted with water, and then extracted with $CHCl_3$. The extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was identified as the starting material (IX) by the IR spectrum.

Desacetyl yuzurimine-A (XII). A soln of yuzurimine-A (as hydrochloride, 38 mg) in 10% HCl–MeOH (10 ml) was refluxed for 17 hr. After cooling, the soln was concentrated under reduced press to give white crystals. Recrystallization from MeOH-ether afforded colourless plates of XII (as hydrochloride, 30 mg, 87%); m.p. 251–254° (in a sealed tube); ν_{max}(nujol) 3370, 3140 and 1724 cm^{-1}; *m/e* 387 (9, M$^+$-HCl), 369 (93), 354 (33), 340 (36), 326 (44) and 310 (100). (Found: C, 64·54; H, 8·24; N, 3·25. $C_{23}H_{33}O_4N$·HCl requires: C, 65·15; H, 8·08; N, 3·30%).

Acetylation of yuzurimine-B (XIV). A soln of XIV (as hydrochloride, 50 mg) in Ac_2O-pyridine (1:1, 1 ml) was allowed to stand at room temp overnight, and then concentrated under reduced press to give a viscous oil, which was converted to the corresponding crystalline hydrochloride with MeOH containing HCl. Recrystallization from MeOH-ether afforded colourless plates of XIII (as hydrochloride, 45 mg, 82%); m.p. 266–267·5°; ν_{max}(KBr) 2600(br), 1737, 1240 and 1032 cm^{-1}; δ 1·13 (3H, d, J = 6 Hz), 2·08 (3H, s), 3·70 (3H, s) and 4·47 (2H, s) ppm; *m/e* 413 (100, M$^+$-HCl), 370 (35), 353 (52) and 340 (34). (Found: C, 66·78; H, 8·04; N, 3·25. $C_{25}H_{35}O_4N$·HCl requires: C, 66·72; H, 8·06; N, 3·11%).

Zinc reduction of yuzurimine (II). A soln of II (2.886 g) in AcOH·(40 ml) was heated with active Zn powder (8 g) at 90–95° for 2 hr with stirring, and then cooled. After the Zn powder was removed by filtration, the filtrates were concentrated under reduced press to give an oil, which was dissolved in $CHCl_3$ (100 ml). The $CHCl_3$ soln was washed with NaOH aq and water, and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from isopropyl ether to afford white crystals of XVI (2·294 g, 82%). Recrystallization from cyclohexane gave colourless plates; m.p. 132–134°; ν_{max}(nujol) 1749, 1730, 1254 and 1247 cm^{-1} (no OH band); δ 1·16 (3H, d, J = 6 Hz), 1·99 (6H, s), 3·59 (3H, s), 4·33 (2H, t, J = 12 Hz) and 5·31 (1H, q, J = 11 and 7 Hz) ppm; *m/e* 471 (100, M$^+$), 440 (4), 428 (28), 412 (69) and 398 (12). (Found: C, 68·83; H, 7·93; N, 2·68. $C_{27}H_{37}O_6N$ requires: C, 68·76; H, 7·91; N, 2·97%).

Desacetyl desoxy-yuzurimine (XVIII). A soln of desoxy-yuzurimine (700 mg) in 7% HCl–MeOH (30 ml) was refluxed for 8 hr. After cooling the soln was concentrated under reduced press to give white crystals of XVIII (501 mg, 80%). Recrystallization from MeOH gave colourless plates; m.p. 271–273° (as hydrochloride, in a sealed tube); ν_{max}(nujol) 3370, 1732, 1191, 1163 and 1046 cm^{-1}; *m/e* 387 (100, M$^+$-HCl), 370 (24) and 356 (41). (Found: C, 65·08; H, 8·56; N, 3·38. $C_{23}H_{33}O_4N$·HCl requires: C, 65·15; H, 8·08; N, 3·30%).

Zinc reduction of desacetyl yuzurimine (V). A soln of V (as hydrochloride, 420 mg) in AcOH (8 ml) was heated with active Zn powder (2 g) at 97–103° for 2 hr with stirring, and then cooled. After the Zn powder was removed by filtration, the filtrates were concentrated under reduced press to give an oil, which was dissolved in $CHCl_3$. The soln was successively washed with NaOH aq and with water, and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was dissolved in a small amount of MeOH containing HCl. The resulting soln was concentrated under reduced press to give colourless crystals of XVIII (263 mg, 65%) (m.p. and IR spectrum).

Formation of the sulfite (XIX). $SOCl_2$ (0·3 ml) was added to a suspension of XVIII (as hydrochloride, 150 mg) in DMF (3 ml) cooled in an ice-bath. The soln was allowed to stand at 0–4° for 15 hr and at room temp for 2 hr, and then poured into NaOH aq. The aqueous soln was extracted with $CHCl_3$. The extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced press to give a solid, which was recrystallized from acetone to afford colourless plates of XIX (99 mg, 67%), m.p. 214–217°; ν_{max}(nujol) 1734, 1203, 1189, 1180, 972, 932, 871 and 749 cm^{-1}; δ 1·11 (3H, d, J = 6 Hz), 3·68 (3H, s), 4·33 (1H, d, J = 13 Hz), 5·3 (1H, m) and 5·39 (1H, d, J = 13 Hz) ppm; *m/e* 433 (100, M$^+$), 402 (9), 374 (5), 369 (12) and 340 (28). (Found: C, 63·60; H, 7·06; N, 3·23. $C_{23}H_{31}O_5NS$ requires: C, 63·71; H, 7·21; N, 3·23%).

Formation of the dimesylate (XX). Mesyl chloride (1 ml) was added to a suspension of XVIII (as hydrochloride, 552 mg) in dry pyridine (5 ml) cooled in an ice-bath. The soln was stirred at 0° for 3 hr and at room temp overnight, and then poured into water. The aqueous soln was made basic pH > 10) with 20% NaOH aq and extracted with ether. The extracts were successively washed with water, and sat NaCl aq,

and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from MeOH to afford slightly coloured crystals of the dimesylate (XX; 479 mg, 68%). Recrystallization from MeOH gave colourless needles; m.p. 155–157°; ν_{max}(nujol) 1725, 1351, 1332, 1318, 1175, 1168, 976, 925, 891 and 840 cm^{-1}; δ 1·10 (3H, d, J = 6 Hz), 3·14 (6H, s), 3·64 (3H, s), 4·64 (2H, s) and 5·16 (1H, q, J = 11 and 6 Hz), ppm; *m/e* 543 (21, M^+), 512 (2), 464 (22), 447 (98), 416 (8), 388 (7), 368 (100) and 352 (56). (Found: C, 55·15; H, 6·73; N, 2·19. $C_{25}H_{37}O_8NS_2$ requires: C, 55·22; H, 6·86; N, 2·58%).

Formation of the monomesylate (XXI). To a soln of XX (371 mg) in DMF (2·5 ml) was added lithium chloride (*ca* 500 mg). The soln was warmed at 90–100° for 18 hr. After cooling, the soln was poured into NaOH aq and extracted with $CHCl_3$. The extracts were washed with water and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was dissolved in a small amount of 7% HCl–MeOH. The soln was concentrated under reduced press to give an oil, which was crystallized from acetone to afford white crystals of XXI (170 mg, 51%). Recrystallization from MeOH-ether gave colourless needles; m.p. 253–254° (as hydrochloride, in a sealed tube); ν_{max}(nujol) 1730, 1637, 1355, 1207, 1179, 956 and 835 cm^{-1}; δ 1·27 (3H, d, J = 7 Hz), 3·13 (3H, s), 3·64 (3H, s), 4·73 (2H, s) and 5·93 (2H, s) ppm; *m/e* 447 (89, M^+-HCl), 416 (13), 388 (11), 368 (100), 352 (38) and 338 (14). Found: C, 59·52; H, 6·99; N, 2·89. $C_{24}H_{33}O_5NS$·HCl requires: C, 59·55; H, 7·08; N, 2·89%).

Catalytic reduction of the monomesylate (XXI). A soln of XXI (as hydrochloride, 145 mg) in MeOH (10 ml) was stirred with PtO_2 (50 mg) under H_2 atmosphere at room temp for 3 days. After filtration of the catalyst, the filtrates were concentrated under reduced press to give an oil, which was crystallized from MeOH-ether to afford white crystals of XV (109 mg, 75%). Recrystallization from MeOH-ether gave colourless plates; m.p. 225–227° (as hydrochloride); ν_{max}(KBr) 1724, 1354, 1196, 1175, 945 and 842 cm^{-1}; δ 1·13 (3H, d, J = 6 Hz), 3·08 (3H, s), 3·64 (3H, s), 4·63 (2H, q, J = 16 and 11 Hz) ppm; *m/e* 449 (68, M^+-HCl), 418 (8), 390 (6), 370 (100), 354 (27) and 340 (22). (Found: C, 59·21; H, 7·50; N, 2·96. $C_{24}H_{35}O_5NS$·HCl requires: C, 59·31; H, 7·47; N, 2·88%).

Mesylation of yuzurimine-B (XIV). Mesyl chloride (0·3 ml) was added to a suspension of yuzurimine-B (as hydrochloride, 59 mg) in dry pyridine (1 ml) cooled in an ice-bath. The soln was stirred at 0° for 2 hr and at room temp overnight, and then poured into water. The aqueous soln was made basic (pH > 10) with 10% NaOH aq and extracted with ether. The ethereal layer was washed with water and extracted with aqueous HCl. The acidic soln was made basic again with 10% NaOH aq, and then extracted with ether. The ethereal extracts were washed with water, and sat NaCl aq, and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was dissolved in a small amount of MeOH containing HCl. The soln was concentrated under reduced press to give an oil, which was crystallized from acetone to afford plates of XV (31 mg, 44%) (mixed m.p., IR and mass spectra).

Von Braun degradation of desoxy-yuzurimine (XVI). To a soln of desoxy yuzurimine (1·330 g) in abs benzene (30 ml) was added BrCN (1·1 g) in abs benzene (10 ml). The soln was allowed to stand at room temp overnight, and then washed successively with HCl aq, NaOH aq, water, and sat NaCl aq, and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from benzene-isopropyl ether to afford white crystals of XXII (1·421 g, 87%). Recrystallization from $CHCl_3$-isopropyl ether gave colourless plates; m.p. 188–190°; ν_{max}(KBr) 2200, 1739, 1257, 1246, 1164 and 1029 cm^{-1}; δ 1·18 (3H, d, J = 5 Hz), 1·99 (6H, s), 3·61 (3H, s), 4·44 (2H, t, J = 12 Hz) and 5·26 (1H, q, J = 11 and 7 Hz) ppm; *m/e* 578 and 576 (33 and 35, M^+), 519 (14), 518 (19), 517 (14), 516 (17), 497 (39), 456 (100), 397 (34) and 395 (30). Found: C, 58·47; H, 6·86; N, 4·89. $C_{28}H_{37}O_6N_2Br$ requires: C, 58·23; H, 6·46; N, 4·85%).

Sodium borohydride reduction of the bromo-cyanamide (XXII). To a soln of XXII (549 mg) in DMSO (7 ml) was added $NaBH_4$ (520 mg). The soln was stirred at room temp overnight, and then poured into water. The aqueous soln was extracted with ether. The extracts were washed with water and then with sat NaCl aq, and dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from MeOH to afford white crystals of the cyanamide (XXIV; 353 mg, 75%). Recrystallization from MeOH gave colourless plates; m.p. 208–210°; ν_{max}(KBr) 2200, 1732, 1264, 1252 and 1029 cm^{-1}; δ 0·99 (3H, d, J = 5 Hz), 1·05 (3H, d, J = 5 Hz), 1·99 (6H, s), 3·61 (3H, s), 4·34 (2H, q, J = 14 and 12 Hz) and 5·30 (1H, br. d, J = 11 Hz) ppm; *m/e* 498 (100, M^+), 455 (11), 439 (48), 438 (41), 395 (16) and 379 (43). (Found: C, 67·70; H, 7·84; N, 5·58. $C_{28}H_{38}O_6N_2$ requires: C, 67·44; H, 7·68; N, 5·62%).

Dehydrobromination of the bromo-cyanamide (XXII). To a soln of XXII (208 mg) in dry pyridine (5 ml) was added AgF (*ca* 500 mg). The soln, which was protected from light, was stirred at room temp for 4 days, and then poured into water. The aqueous soln was extracted with ether. The extracts were washed successively with HCl aq, NaOH aq, water and sat NaCl aq, and then dried over Na_2SO_4. The ethereal soln was concentrated under reduced press to *ca* 3 ml, which gave white crystals of XXVI (139 mg, 78%). Recrystalli-

zation from MeOH gave colourless plates; m.p. 186–188°; ν_{max}(KBr) 2200, 1737, 1645, 1250, 1200, 1173 and 1032 cm^{-1}; δ 1·89 (3H, s), 2·00 (6H, s), 3·61 (3H, s), 4·35 (2H, t, J = 12 Hz), 4·90 (1H, br. s), 5·06 (1H, br. s) and 5·29 (1H, q, J = 11 and 7 Hz) ppm; *m/e* 496 (100, M^+), 469 (28), 453 (18), 437 (88) and 377 (48). (Found: C, 67·65; H, 7·54; N, 5·95. $C_{28}H_{36}O_6N_2$ requires: C, 67·72; H, 7·31; N, 5·64%).

Catalytic reduction of XXVI. A soln of XXVI (80 mg) in MeOH (10 ml) was stirred with PtO_2 (16 mg) under H_2 atmosphere at room temp for 2 days. After filtration of the catalyst, the filtrates were concentrated under reduced press to give an oil, which was crystallized from MeOH to afford colourless plates of XXIV (58 mg, 72%) (m.p. and IR spectrum).

Desacetyl bromo-urea (XXVII). A soln of XXII (318 mg) in 17% HCl–MeOH (25 ml) was refluxed for 14 hr. After cooling, the soln was concentrated under reduced press to *ca* 1 ml, and then poured into NaOH aq. The aqueous soln was extracted with $CHCl_3$. The extracts were washed with water, and then dried over Na_2SO_4. The organic layer was concentrated under reduced press to *ca* 3 ml, which gave white crystals of XXVII (188 mg, 67%). Recrystallization from $CHCl_3$ afforded colourless plates; m.p. 186–188°; ν_{max}(nujol) 3460, 3340, 3260, 3210, 1724, 1656, 1579 and 1170 cm^{-1}; *m/e* 512 and 510 (4 and 4, M^+), 466 (18), 387 (78), 370 (20), 356 (30) and 149 (100) (Found: C, 56·17; H, 6·92; N, 5·26. $C_{24}H_{35}O_5N_2Br$ requires: C, 56·36; H, 6·90; N, 5·48%).

Desacetyl urea (XXVIII). A soln of XXIV (153 mg) in 17% HCl–MeOH (7 ml) was refluxed for 13 hr. After cooling, the soln was concentrated under reduced press to give an oil, which was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with NaOH aq and water, and then dried over Na_2SO_4. The solvent was removed under reduced press to give a white solid, which was crystallized from acetone to afford colourless crystals of XXVIII (68 mg, 51%). Recrystallization from MeOH gave needles, m.p. 148–150°; ν_{max}(nujol) 3580, 3480, 3320, 3250, 3200, 1724, 1649, 1573, 1200, 1178. 1015 and 860 cm^{-1}; *m/e* 432 (82, M^+), 415 (14), 401 (13) and 149 (100). Found: C, 66·44; H, 8·35; N, 6·58. $C_{24}H_{36}O_5N_2$ rrquires: C, 66·64; H, 8·39; N, 6·48%).

Reaction of the bromo-cyanamide (XXII) *with* AcOH. A soln of XXII (259 mg) in AcOH (15 ml) was refluxed for 22 hr. After cooling, the soln was concentrated under reduced press to give an oil, which was dissolved in a small amount of MeOH and poured into water. The aqueous soln was extracted with benzene. The extracts were washed successively with NaOH aq, water and sat NaCl aq, and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from acetone-ether to afford white crystals of XXIX (19 mg, 7%). Recrystallization from acetone-ether gave colourless needles; m.p. 215–220° (dec); ν_{max}(nujol) 3470, 3350, 1723, 1665, 1638, 1593, 1256, 1247 and 1193 cm^{-1}; *m/e* 596 and 594 (16 and 16, M^+), 550 (29), 471 (100), 428 (29) and 412 (72). Found: C, 56·46; H, 7·01; N, 4·96. $C_{28}H_{39}O_7N_2Br$ requires: C, 56·47; H, 6·60; N, 4·71%). The aqueous soln was made basic (pH > 10) with 20% NaOH aq, and then extracted with $CHCl_3$. The extracts were washed with water, and dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from isopropyl ether to afford colourless plates of XVI (137 mg, 65%) (m.p. and IR spectrum).

Reaction of the cyanamide (XXIV) *with* AcOH *saturated with* HCl *gas.* A soln of XXIV (370 mg) in AcOH (20 ml) saturated with HCl gas was refluxed for 46 hr. After cooling, the soln was concentrated under reduced press to give an oil, which was dissolved in a small amount of MeOH and poured into water. The aqueous soln was extracted with ether. The extracts were washed successively with NaOH aq, water and sat NaCl aq, and then dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was crystallized from ether-isopropyl ether to afford white crystals of XXX (73 mg, 19%). Recrystallization from acetone-isopropyl ether gave colourless plates; m.p. 215–218°; ν_{max}(nujol) 3500, 3410, 1743, 1730, 1658, 1600, 1425, 1263, 1248, 1197, 1176 and 1021 cm^{-1}; δ 0·91 (3H, d, J = 6 Hz), 1·00 (3H, d, J = 6 Hz), 2·00 (6H, s), 3·60 (3H, s), 4·32 (2H, s), 4·0–5·9 (2H, br. m) and 5·30 (1H, m) ppm; *m/e* 516 (100, M^+), 499 (15), 485 (8) and 457 (18). (Found: C, 64·67; H, 7·25; N, 5·42. $C_{28}H_{40}O_7N_2$ requires: C, 65·09; H, 7·80; N, 5·4%). The aqueous soln was made basic (pH > 10) with 10% NaOH aq, and then extracted with $CHCl_3$. The extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced press to give an oil, which was chromatographed on silicic acid (5 g). Elution with 1% MeOH-$CHCl_3$ gave an oil of XXXI (170 mg, 49%); ν_{max}(film) 3350, 1730, 1252, 1166 and 1027 cm^{-1}; δ 0·96 (6H, d, J = 5 Hz), 2·01 (6H, s), 3·64 (3H, s), 4·36 (2H, br. s) and 5·30 (1H, m) ppm. This compound (XXXI) was directly used for the next experiment.

Hydrolysis of the amine (*XXXI*). NaOH (120 mg) in abs MeOH (3 ml) was added to a soln of XXXI, which was obtained from 336 mg of XXIV, in abs MeOH (1 ml). The soln was allowed to stand at room temp overnight, and then poured into water. The aqueous soln was extracted with $CHCl_3$. The extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced press to give a white solid, which was crystallized from acetone to afford crystals of XXXII (78 mg, 30% from XXIV). Recrystal-

lization from MeOH gave colourless needles; m.p. 212–214° (in a scaled tube); ν_{max}(KBr) 3480, 3310, 1738-(sh), 1713, 1201, 1172, 1046 and 1026 cm^{-1}; *m/e* 389 (100, M^+), 358 (79), 346 (6), 330 (6), 329 (8), 328 (9) and 327 (10). (Found: C, 70·94; H, 9·34; N, 3·66. $C_{23}H_{35}O_4N$ requires: C, 70·92; H, 9·06; N, 3·60%).

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