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Protoplumericin, an Iridoid Bis-glucoside in *Allamanda neriifolia*

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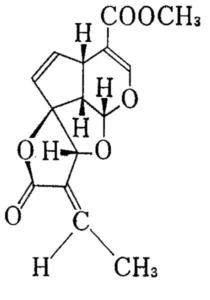
Protoplumericin, 13-O-(β-D-glucopyranosyl-*p*-coumaroyl)-plumieride (IV), was isolated from the polar fraction of the MeOH percolate of *Allamanda neriifolia* Hook by means of several column chromatographies and droplet counter current chromatography. Enzymatic and alkaline transformations of IV into plumericin (I) and plumieride (III), respectively, were carried out.

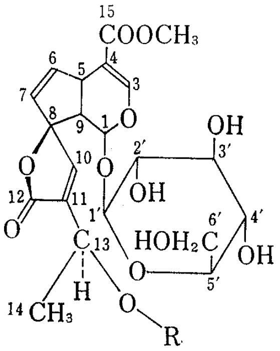
Keywords——iridoid; iridoid bis-glucoside; plumericin; plumieride; Apocynaceae; *Allamanda*; tetracyclic iridoid lactone; iridoid *p*-coumaroate

The constituents of *Allamanda cathartica* L. were investigated by Kupchan *et al.*[1)] Antileukemic tetracyclic iridoid lactones including allamandin and the already known compounds plumericin and isoplumericin,[2)] were isolated from the less polar fraction of the extract, in addition to weakly active allamandicin and allamdin, and their structures were elucidated. The polar fraction, however, was not examined, probably because of its low activity against KB tissue culture. In 1976, plumieride[3)] was also detected in the same plant by Inouye *et al.*[4)] by means of GC–MS. In this paper, we describe the isolation and properties of protoplumericin, a glucosyl-*p*-coumaroyl plumieride obtained from the stem of *Allamanda neriifolia* Hook.

The methanol percolate of the dried powdered stem was partitioned successively with benzene, chloroform and then butanol. From the benzene layer, plumericin (I) was isolated in a yield of 0.02%. The chloroform layer showed, on thin layer chromatography (TLC), one spot (II) which afforded the same yellow staining with H_2SO_4 as I. The amount obtained was not sufficient for further investigation, however. In the butanol layer, two major con-



I (plumericin)



III (plumieride) : R=H

IV (protoplumericin) :

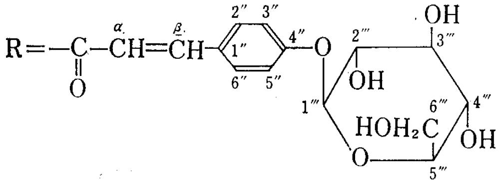


Chart 1

stituents were found on TLC and isolated by a combination of chromatographies, *i.e.* Amberlite XAD-2/H_2O–MeOH, silica gel/$CHCl_3$–MeOH–H_2O or $CHCl_3$–MeOH, and droplet counter current chromatography (DCCC) with $CHCl_3$–MeOH–H_2O. The less polar substance was identified as a plumieride (III) (yield, 0.08%) by comparison of the physical constants and the ^1H-nuclear magnetic resonance (^1H-NMR) spectrum with those of an authentic sample.[3-5]

The most polar and major substance was isolated as a solid in a yield of 0.83%, showing staining similar to that of I, II or III on TLC and was named protoplumericin (IV). On comparison of the ^1H-NMR spectrum with that of III, IV exhibited olefinic protons at δ 6.69 and 7.96 with a coupling constant of 16 Hz, and four protons at δ 7.33 and 7.60, both as two-proton doublets ($J=7$ Hz), in addition to most of the resonances that appeared in the spectrum of III. The ultraviolet (UV) spectrum showed absorption maxima at 210, 222, 290 (sh), 296 and 305 nm. On the basis of the ^1H-NMR and UV spectra, IV seemed to have a *p*-coumaric acid (V) moiety, and the presence of V in the structure of IV was also suggested by the ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectrum, in which carbons originating from V were found at δ 116.2, 117.0($\times$2), 128.4, 130.3($\times$2), 145.3, 160.2, 166.2 (C=O). The ^{13}C-NMR spectrum of IV also disclosed, along with all the carbons due to III, a second glucosyl residue with resonances at δ 62.2, 71.1, 74.8, 78.4 and 101.6 (anomeric), most of which, except for the anomeric carbon, almost duplicated those of the other glucose linked at the 1-hydroxyl group in the plumieride moiety. IV was therefore considered to be a glucoside of III-*p*-coumaroate, in which the glucosyl-*p*-coumaroyl group is probably attached to the 13-hydroxyl group of III, since a downfield shift was observed in C-13, and upfield shifts were seen in the adjacent C-11 and C-14, in comparison with the signals of III.

In order to confirm the location of the *p*-coumaroyl and the second glucosyl groups in IV, enzymatic and alkaline hydrolyses of IV were attempted. Upon enzymatic hydrolysis of IV for 1 h with β-glucosidase (Cellulase, type I), six products were detected by TLC and named IV-1—IV-6 in order of increasing polarity. They were isolated by means of column chromatography. IV-1, IV-3 and IV-5 were identified as I, V and III, respectively. IV-2, obtained in a small amount as a solid, was also isolated as a major product when III was treated with Cellulase, and was found to be the aglycone of III by comparison of the ^1H- and ^{13}C-NMR spectra of IV-2 (=III-1) and III.

IV-4 had the same *Rf* value as II on TLC, and was hydrolyzed with Cellulase to give I. The *p*-coumaroyl residue in IV-4 was apparent in the ^1H- and ^{13}C-NMR spectra. In the ^{13}C-NMR spectrum, deshielding of the C-13 carbinyl carbon was considered to be due to 13-O-acylation, as in IV. The peak at δ 101.6 due to the anomeric carbon of the second glucose in the ^{13}C-NMR of IV was no longer apparent. IV-4 was therefore identified as the *p*-coumaroate of III.

IV-6, the most polar product, was esterified with diazomethane, showing presence of a carboxyl residue. The methyl ester of IV-6 (IV-7) was also obtained from IV together with III when IV was treated with NaOMe, and IV-6 was identified as methyl glucosyl-*p*-coumaroate on the basis of the ^1H- and ^{13}C-NMR spectra. The glucosidic linkage was found to be β, since the anomeric proton was observed at δ 5.70 as a doublet of 6 Hz.

In view of the evidence from the hydrolysis of IV, especially the occurrence of IV-4, IV-5 (=III) and IV-6, the structure of IV was established as 13-O-(β-D-glucopyranosyl-*p*-coumaroyl)-plumieride.

IV appears to be the genuine glycoside of I in this plant, since the yield of I is quite low in comparison with that of IV, and IV is transformed into I immediately upon treatment with β-glucosidase. In order to obtain antileukemic iridoid lactones such as I from *Allamanda neriifolia* and possibly from *A. cathartica*, therefore, enzymatic preparation from the genuine glycosides in the butanol extractives may be a better procedure than direct isolation of the lactones from the less polar fraction.

Experimental

^{1}H-NMR and ^{13}C-NMR spectra were recorded in pyridine-d_5 unless otherwise mentioned, on Hitachi R-22 and JEOL FX-100 spectrometers, respectively. Chemical shifts are given in δ-values referred to internal tetramethylsilane. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. UV spectra were taken on Shimadzu 200S double beam spectrophotometer. Melting points were measured on a Kofler block and are uncorrected. The following solvent systems were used for column, thin layer and DCC chromatographies: solv. 1, $CHCl_3$–MeOH–H_2O (7: 3: 1), lower layer; solv. 2, (7: 2: 1); solv. 3, (5: 6: 4) (for DCCC); solv. 4, $CHCl_3$–MeOH (10: 1—5: 1); solv. 5, benzene–acetone. As a spray reagent for TLC, 10% H_2SO_4 was used and the plates were charred for detection.

Extraction and Fractionation——Dried powdered stem (1.6 kg) cultivated at Tanegashima Experiment Station of Medicinal Plants, National Institute of Hygienic Sciences, and harvested in July, 1978, was percolated with MeOH. The MeOH percolate was concentrated to 1 l, and diluted with the same volume of H_2O. The deposit was removed by filtration and the filtrate was extracted successively with benzene (ext. 3.9 g), $CHCl_3$ (7.1 g) and BuOH (33.3 g).

Plumericin (I)——The first fraction from silica gel column chromatography of the benzene extractives with solv. 5 was crystallized from MeOH to give prisms (420 mg), mp 210—216°C (dec.), $[\alpha]_D^{25}$ +178.6° (c=0.23, $CHCl_3$) (ref. mp 211.5—212.5°C, $[\alpha]_D^{25}$ +197.5°),2) λ_{max}^{MeOH} nm (ε): 212 (32600), 240 (sh) (19200). ^{1}H-NMR ($CDCl_3$): 2.09 (3H, d, J=7 Hz, 14-CH_3), 3.44 (1H, dd, J=6, 9 Hz, 9-H), 3.79 (3H, s, $-COOCH_3$), 4.03 (1H, td, J=2, 9 Hz, 5-H), 5.13 (1H, bs, 10-H), 5.59 (1H, d, J=6 Hz, 1-H), 5.66 (1H, dd, J=2, 6 Hz, 7-H), 6.07 (1H, dd, J=2, 6 Hz, 6-H), 7.18 (1H, dq, J=2, 7 Hz, 13-H), 7.47 (1H, s, 3-H). ^{13}C-NMR: 15.9 (q, C-14), 38.8 (d, C-5), 51.4 (q, $-COO\underline{C}H_3$), 53.9 (d, C-9), 80.5 (d, C-10), 102.8 (d, C-1), 105.0 (s, C-8), 110.0 (s, C-4), 127.2 (d, C-13), 128.3 (s, C-11), 141.0 (d, C-6), 144.7 (d, C-7), 153.0 (d, C-3), 168.4 (s, C-15), 177.7 (s, C-12). The ^{1}H-NMR spectrum was in good agreement with those reported by Kupchan *et al.*1) and Albers-Schönberg *et al.*2)

Subst. II——The $CHCl_3$ fraction was chromatographed on a silica gel column with solv. 4, and then on an XAD-2 column with 50% MeOH. The fraction containing Subst. II was finally chromatographed on silica gel with solv. 2 to give 30 mg of a homogeneous solid (II), which showed polarity almost intermediate between those of I and III on TLC with solv. 2.

Plumieride (III)——The BuOH layer was dissolved in H_2O and subjected to column chromatography on XAD-2. Elution was carried out with H_2O–MeOH, with increasing MeOH concentration. The 30% MeOH effluent yielded a solid which was further purified on a silica gel column with solv. 1, and finally by DCCC with solv. 3 (ascending method). On crystallization from EtOAc–MeOH, prisms (1.3 g) were obtained, mp 228—230°C, $[\alpha]_D^{25}$ −110.2° (c=0.90, H_2O), λ_{max}^{MeOH} 210 (16300), (ref.: mp 224—225°C, $[\alpha]_D^{16}$ −114° (H_2O)).3) ^{1}H-NMR: 1.61 (3H, d, J=6 Hz, 14-CH_3), 3.06 (1H, dd, J=6, 8 Hz, 9-H), 3.63 (3H, s, $-COOCH_3$), 3.80—4.50 (~8H, m), 4.76 (1H, dq, J=2, 6 Hz, 13-H), 5.32 (1H, d, J=7 Hz, 1′-H), 5.40 (1H, dd, J=2, 6 Hz, 7-H), 5.58 (1H, d, J=6 Hz, 1-H), 6.44 (1H, dd, J=2, 6 Hz, 6-H), 7.60 (1H, d, J=2 Hz, 3-H), 7.90 (1H, d, J=2 Hz, 10-H). The ^{1}H-NMR chemical shifts were in good agreement with those of the authentic plumieride.4) ^{13}C-NMR: 23.0 (q, C-14), 40.1 (d, C-5), 49.9 (d, C-9), 51.3 (q, $-COO\underline{C}H_3$), 62.1 (t, C-6′), 62.7 (d, C-13), 70.7 (d, C-4′), 74.7 (d, C-2′), 78.1 (d, C-3′), 78.7 (d, C-5′), 94.0 (d, C-1), 96.4 (s, C-8), 100.8 (d, C-1′), 109.5 (s, C-4), 129.1 (d, C-10), 138.7 (s, C-11), 140.9 (d, C-6), 149.1 (d, C-7), 152.0 (d, C-3), 166.7 (s, C-15), 171.3 (s, C-12). The ^{13}C-NMR chemical shifts were in good agreement with those of plumieride reported by Chaudhri *et al.*5)

Enzymatic Hydrolysis of III——A soln. of 300 mg of III in 5 ml of H_2O was shaken at 38°C with 1.5 g of Cellulase (Sigma Chem. Co. Ltd., type I), for 4.5 h. The mixture was extracted with $CHCl_3$ and the $CHCl_3$ layer was concentrated *in vacuo*. The residue was chromatographed on a silica gel column with solv. 2 to give 68 mg of a homogeneous solid (III-1), $[\alpha]_D^{20}$ +4.9° (c=2.1, MeOH). ^{1}H-NMR ($CDCl_3$): 1.43 (3H, d, J=6 Hz, 14-CH_3), 2.97 (1H, dd, J=4, 8 Hz, 9-H), 3.76 (3H, s, $-COOCH_3$), 3.89 (1H, dd, J=2, 8 Hz, 5-H), 4.64 (1H, q, J=6 Hz, 13-H), 5.04 (1H, d, J=4 Hz, 1-H), 5.44 (1H, dd, J=2, 6 Hz, 7-H), 6.02 (1H, dd, J=2, 6 Hz, 6-H), 7.03 (1H, s, 3-H), 7.39 (1H, s, 10-H). ^{13}C-NMR: 23.0 (q, C-14), 39.4 (d, C-5), 51.1 (q, $-COO\underline{C}H_3$), 51.5 (d, C-9), 62.8 (d, C-13), 92.7 (d, C-1), 96.7 (s, C-8), 109.2 (s, C-4), 129.6 (d, C-10), 139.1 (s, C-11), 140.4 (d, C-6), 148.7 (d, C-7), 152.5 (d, C-3), 167.0 (s, C-15), 171.3 (s, C-12).

Protoplumericin (IV)——The fraction next to III on XAD-2 column chromatography of the BuOH extractives with 30—50% MeOH, was subjected to silica gel column chromatography with solv. 1, and finally to DCCC with solv. 3. The most polar and major compound (IV), which showed the same staining as I, II or III on a TLC plate upon heating with H_2SO_4, was obtained as a solid (13.2 g), $[\alpha]_D^{25}$ −89.9° (c=1.09, MeOH). *Anal.* Calcd for $C_{36}H_{42}O_{19} \cdot H_2O$: C, 54.27; H, 5.57. Found: C, 54.65; H, 5.83. λ_{max}^{MeOH} 210 (27000), 222 (29900), 290 (sh) (25000), 296 (27200), 305 (27700). ^{1}H-NMR: 1.62 (3H, d, J=7 Hz, 14-CH_3), 3.03 (1H, dd, J=6, 7 Hz, 9-H), 3.61 (3H, s, $-COOCH_3$), 3.80—4.60 (~18H, m), 5.29 (1H, d, J=6 Hz, 1′-H), 5.43 (1H, dd, J=2, 5 Hz, 7-H), 5.63 (1H, d, J=6 Hz, 1-H), 6.09 (1H, dq, J=2, 6 Hz, 13-H), 6.48 (1H, dd, J=2, 5 Hz, 6-H), 6.69 (1H, d, J=16 Hz, α-H), 7.33 (2H, d, J=7 Hz, 3″- and 5″-H), 7.60 (2H, d, J=7 Hz, 2″- and 6″-H), 7.66 (1H, d, J=2 Hz, 3-H), 7.96 (1H, d, J=16 Hz, β-H), 8.03 (1H, d, J=2 Hz, 10-H). ^{13}C-NMR: 19.3 (q, C-14), 40.3 (d, C-5), 50.2 (d, C-9), 51.2 (q, $-COO\underline{C}H_3$), 62.2 (t, C-6′ and -6‴), 65.1 (d, C-13), 71.7 (d, C-4′ and -4‴), 74.8 (d, C-2′ and -2‴), 78.2 (d, C-3′), 78.4 (d, C-3‴), 78.9 (d, C-5′ and -5‴), 93.7 (d, C-1), 96.7 (s, C-8), 100.5 (d, C-1′), 101.6 (d, C-1‴), 109.3 (s, C-4), 116.2 (d, C-α), 117.0 (d, C-3″ and -5″), 128.4

(s, C-1″), 128.4 (d. C-10), 130.3 (d, C-2″ and 6″), 133.6 (s, C-11), 141.7 (d, C-6), 145.3 (d, C-β), 150.8 (d, C-7), 152.1 (d, C-3), 160.2 (s, C-4″), 166.2 (s, –CH=CH–$\underline{\mathrm{C}}$OOR), 166.6 (s, C-15), 170.2 (s, C-12).

IV•Acetate——IV (200 mg) was acetylated with 2 ml each of pyridine and Ac$_2$O at room temp. for 20 h, and the acetate was purified on a silica gel column with solv. 5. IV·acetate (50 mg) was obtained as a homogeneous solid, $[\alpha]_{\mathrm{D}}^{25}$ $-47.9°$ ($c=1.34$, MeOH). *Anal.* Calcd for $C_{52}H_{58}O_{27}$: C, 56.01; H, 5.24. Found: C, 55.59; H, 5.23. ^{1}H-NMR (CDCl$_3$): 1.59 (3H, d, $J=7$ Hz, 14-CH$_3$), 1.92, 2.00, 2.02, 2.03, 2.05 (8×OAc), 3.17 (1H, dd, $J=2$, 8 Hz, 9-H), 3.78 (3H, s, –COOCH$_3$), 3.60—3.80 (3H, m), 4.00—4.50 (4H, m), 4.80—5.30 (9H, m), 5.48 (1H, dd, $J=1.5$, 6 Hz, 7-H), 5.76 (1H, dq, $J=1.5$, 7 Hz, 13-H), 6.38 (1H, d, $J=16$ Hz, α-H), 6.46 (1H, dd, $J=3$, 6 Hz, 6-H), 7.02 (1H, d, $J=2$ Hz, 3-H), 7.03 (2H, d, $J=8$ Hz, 3″- and 5″-H), 7.41 (1H, d, $J=2$ Hz, 10-H), 7.53 (2H, d, $J=8$ Hz, 2″- and 6″-H), 7.69 (1H, d, $J=16$ Hz, β-H).

Enzymatic Hydrolysis of IV——IV (2.9 g) was dissolved in H$_2$O (50 mg) and shaken with Cellulase (type I, 3 g) at 38°C for 1 h. The mixture was diluted with H$_2$O and extracted with BuOH. The BuOH ext. was fractionated on silica gel columns with solv. 1, solv. 2 and solv. 4, successively. From the least polar fraction, 76 mg of IV-1, mp 210—212°C (dec.), was obtained and identified as I by comparison (TLC, IR and mixed fusion) with authentic I. The mother liq. fraction and the fraction containing the next most polar compound (IV-2) (590 mg) were combined and subjected to column chromatography with solv. 4 to give, besides 50 mg of IV-1, 10 mg of IV-2 as a solid. The ^{1}H-NMR spectrum and *Rf* value on TLC were in good agreement with those of III-1 obtained by the enzymatic hydrolysis of III.

The third compound (IV-3) was obtained by column chromatography with solv. 2, followed by crystallization from ether to give 7 mg of prisms, mp 207—210°C (dec.). On admixture with *p*-coumaric acid (V), no melting point depression was observed, and IR and UV spectra of the two samples were in good agreement.

The fraction containing the fourth compound (IV-4) was further purified on a silica gel column with solv. 2 to give IV-4 as a solid (200 mg), $\lambda_{\max}^{\mathrm{MeOH}}$ 208 (21100), 225 (18400), 290 (sh) (11500), 300 (13800), 312 (15700). ^{1}H-NMR: 1.63 (3H, d, $J=6$ Hz, 14-H), 3.04 (1H, dd, $J=6$, 7 Hz, 9-H), 3.67 (3H, s, –COOCH$_3$), 3.80—4.60 (8H, m), 5.19 (1H, dd, $J=2$, 6 Hz, 7-H), 5.19 (1H, d, $J=7$ Hz, 1′-H), 5.63 (1H, d, $J=6$ Hz, 1-H), 6.11 (1H, dd, $J=2$, 7 Hz, 13-H), 6.47 (1H, dd, $J=2$, 6 Hz, 6-H), 6.71 (1H, d, $J=16$ Hz, α-H), 7.16 (2H, d, $J=8$ Hz, 3″- and 5″-H), 7.64 (2H, d, $J=8$ Hz, 2″- and 6″-H), 7.66 (1H, d, $J=2$ Hz, 3-H), 8.02 (1H, d, $J=2$ Hz, 10-H), 8.06 (1H, d, $J=16$ Hz, β-H). ^{13}C-NMR: 19.4 (q, C-14), 40.3 (d, C-5), 50.2 (d, C-9), 51.2 (q, –COO$\underline{\mathrm{C}}$H$_3$), 62.4 (t, C-6′), 65.0 (d, C-13), 71.3 (d, C-4′), 74.8 (d, C-2′), 78.2 (d, C-3′), 79.0 (d, C-5′), 93.7 (d, C-1), 96.7 (s, C-8), 100.5 (d, C-1′), 109.3 (s, C-4), 114.5 (d, C-α), 116.8 (d, C-3″ and -5″), 125.9 (s, C-1″), 128.4 (s, C-10), 130.8 (d, C-2″ and -6″), 133.7 (s, C-11), 141.7 (d, C-6), 146.0 (d, C-β), 150.8 (d, C-7), 152.1 (d, C-3), 161.5 (s, C-4″), 166.5 (s, C-15), 166.6 (s, –CH=CH–$\underline{\mathrm{C}}$OOR), 170.3 (s, C-12). On TLC with solv. 2, 3 and 4, IV-4 gave *Rf* values identical with those of II.

IV-4 (10 mg) in 30% EtOH was shaken at 38°C with Cellulase (type I, 20 mg) for 1 h, and the mixture was extracted with CHCl$_3$. The CHCl$_3$ ext. was crystallized from EtOAc–hexane to give prisms, mp 209—211°C, which were identified as I by comparison (melting point, IR and *Rf* on TLC) with an authentic sample.

The fraction containing IV-5 was collected and purified on a silica gel column to give a homogeneous solid, which was further purified by DCCC with solv. 3, and finally crystallized from EtOAc to give 10 mg of prisms, mp 229—230°C. On admixture with III, no melting point depression was observed and the *Rf* and IR spectra of the two samples were in good agreement.

The most polar fraction (60 mg) was dissolved in MeOH and methylated with CH$_2$N$_2$ in ether and the product was purified by column chromatography with solv. 2, followed by crystallization from EtOH to give 10 mg of needles (IV-7), mp 165—167°C, $\lambda_{\max}^{\mathrm{MeOH}}$ 224 (13800), 295 (30100). ^{1}H-NMR: 3.77 (3H, s, –COOCH$_3$), 4.00—4.60 (~6H, m), 5.70 (1H, d, $J=6$ Hz, anomeric), 6.58 (1H, d, $J=16$ Hz, α-H of *p*.c.a.), 7.34 (2H, d, $J=8$ Hz, 3- and 5-H of *p*.c.a.), 7.56 (2H, d, $J=16$ Hz, 2- and 6-H of *p*.c.a.), 7.87 (1H, d, $J=16$ Hz, β-H of *p*.c.a.). ^{13}C-NMR: 5.14 (q, –COO$\underline{\mathrm{C}}$H$_3$), 62.3 (t, C-6‴), 71.2 (d, C-4‴), 74.9 (d, C-2‴), 78.5 (d, C-3‴), 79.0 (d, C-5‴), 101.7 (d, C-1‴), 116.4 (d, C-α), 117.2 (d, C-3″ and -5″), 128.5 (s, C-1″), 130.1 (d, C-2″ and -6″), 144.5 (d, C-β), 160.2 (s, C-4″), 167.4 (s, –$\underline{\mathrm{C}}$OOCH$_3$).

Unreacted IV (*ca.* 50 mg) was recovered from the fraction between IV-5 and IV-6.

Alkaline Hydrolysis of IV——IV (500 mg) was dissolved in 10 ml of MeOH and the solution was mixed with 0.7 ml of methanolic NaOMe (500 mg of Na in 20 ml of MeOH) then allowed to stand for 40 min. The soln. was diluted with MeOH, neutralized with Amberlite IRA 120 and the MeOH was evaporated off *in vacuo*. The residue was fractionated on a silica gel column with solv. 2. Fr. 1 was crystallized from MeOH to give 130 mg of prisms, mp 167—169°C, which were identified as IV-7 by comparison (melting point, and IR and UV spectra) with a sample obtained by enzymatic hydrolysis of IV, followed by CH$_2$N$_2$ methylation. The next fraction was subjected to DCCC and crystallized from EtOAc to give 116 mg of prisms, mp 229—230°C. On admixture with III, no melting point depression was observed, and the ^{1}H-NMR spectra of the two samples were identical.

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Reaction of 1,2,3,4-Tetrahydroquinazolin-4-ones with Acid Anhydride. II[1]

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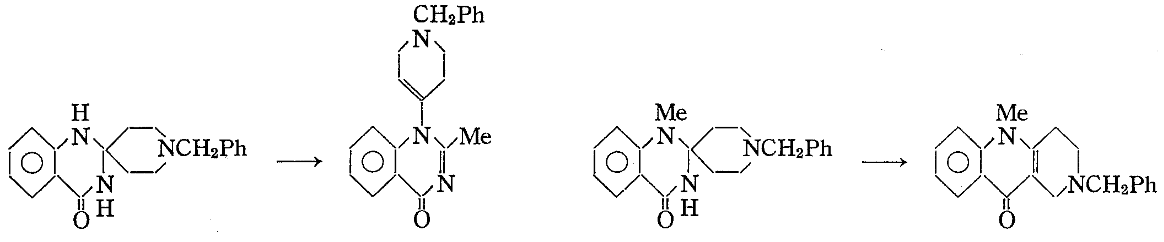
The reaction of 1,2,3,4-tetrahydroquinazoline-2-spirocyclohexan-4-one (**1b**) with acetic anhydride and pyridine gave 1-(1-cyclohexenyl)-2-methyl-1,4-dihydroquinazolin-4-one (**3b**). Compound **3b** gave 3-acetyl-1-(1-cyclohexenyl)-2-methyl-1,2,3,4-tetrahydroquinazolin-4-one (**8b**) upon reduction with $NaBH_4$ followed by acetylation with acetic anhydride. The position of the acetyl group of **8b** was determined by comparison of its NMR spectrum with those of related compounds (**9**, **10**, **11**, **12**, and **13**).

Keywords——4-quinazoline; acetylation; rearrangement; ^1H-NMR; spiro compound

We have previously reported that the reaction of 1-benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-ones (**1a** and **2**) with acetic anhydride and pyridine gives two types (A and B) of rearrangement products (**3a** and **4**), depending upon the presence of absence of a methyl group at the 1′-position of the quinazolines (Chart 1).[1]

Some work has also been done on the acetylation of 1,2,3,4-tetrahydroquinazolin-4-ones; thus, Böhme and Böing reported that the reaction of 2,2-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one with ketene gave 1-acetyl-2,2-dimethyl-1,2,3,4-tetrahydroquinazolin-4-one, while the reaction of the same compound with acetic anhydride and pyridine gave 2-methyl-3,4-dihydroquinazolin-4-one.[2]

Considering our previous result on the reaction of **1** with acetic anhydride and pyridine[1] in connection with the report of Böhme and Böing, the possibility that the structure of the product is not 1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methyl-1,4-dihydroquinazolin-4-one (**3a**) but 3-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methyl-3,4-dihydroquinazolin-4-one (**5**),



1a **3a** **2** **4**

type A rearrangement type B rearrangement

Chart 1