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CONSTITUTION AND SYNTHESIS OF NORANHYDROICARITIN AND ISOANHYDROICARITIN

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Kaempferol (1) when reacted with 2-hydroxy-2-methyl-3-butene in the presence of borontrifluoride etherate yielded a mixture of 6,8-di-(3-methylbut-2-enyl) derivative (2), 4", 5"-dihydro-6", 6"-dimethyl pyrano (2",3" : 7,8)-kaempferol (3) and 8-(3-methylbut-2-enyl) derivative (4). The orientation of alkenyl unit in compound 4 has been unambiguously established and then it agrees in direct comparison with natural noranhydroicaritin. [1] Complete acetylation of 4, followed by reaction of 5 with one mole of methyl iodide in the presence of dry K_2CO_3 and acetone afforded 8-(3-methylbut-2-enyl)-rhamnocitrin triacetate (6) which on deacetylation finally gave natural isoanhydroicaritin [1](7).

Recently Komatsu et al. [1] isolated two new isopentenylated flavonols from the root of Sophora angustifolia Sieb. et Zucc. and named them as isoanhydroicaritin and noranhydroicaritin. Their structures were considered as 8-(3-methylbut-2-enyl) derivatives (7 and 4) of rhamnocitrin and kaempferol respectively by the spectral properties of them and their derivatives. However the location of the isopentenyl unit was not unambiguously established. Noranhydroicaritin was known earlier also as a degradation product of the glycoside noricariin isolated from Epimedium macranthum Morr. et Decne. [2] These flavonols have now been synthesized, thus supporting their constitutions. The synthesis simulates the probable biogenetic pathway in which kaempferol is first isopentenylated in the 8 position and then methylated selectively in the 7 position.

Synthetic kaempferol (1) on reaction with 2-hydroxy-2-methyl-3-butene in the presence of borontrifluoride etherate gave a mixture of three compounds (A, B and C) separable by column chromatography. The product (A) crystallized from benzene-light petroleum mixture as yellow crystals, m.p. 153-55°; R_f 0.67 (Solvent A); green ferric reaction; λ_{max} 272 and 335 nm (logϵ 4.37 and 4.21 respectively); n.m.r. δ 1.78, 1.88 (2s, 12H, $2Me_2C=$), 3.50, 3.64 (2d, J 7Hz, 4H, $2Ar-CH_2$), 5.30 (t, J 7Hz, 2H, $-CH=$), 6.96 (d, J 9Hz, 2H, ArH 3',5') and 8.12 (d, J 9Hz, 2H, ArH 2',6') (Found : C, 70.9; H, 5.8. $C_{25}H_{26}O_6$ requires C, 71.1; H, 6.2%). It formed tetraacetate as white needles, m.p. 144-45°; R_f 0.60 (Solvent D); and trimethyl ether (with 3 moles of dimethyl sulphate in the presence of K_2CO_3 and acetone) as

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yellow needles, m. p. 106-7°; R_f 0.54 (Solvent B); intense green ferric reaction; λmax 277 and 328 nm (logϵ 4.47 and 4.36 respectively); n.m.r. δ 1.71, 1.82 (2s, 12H, $2Me_2C=$), 3.42, 3.54 (2d, J 7Hz, 4H, 2-Ar-CH_2), 3.78, 3.84, 3.88 (3s, 9H, 3MeO), 5.26 (t, J 7Hz, 2H, -CH=), 6.98 (d, J 9Hz, 2H, ArH 3', 5') and 8.04 (d, 9Hz, 2H, ArH 2', 6') (Found : C, 72.5; H, 6.9. $C_{28}H_{32}O_6$ requires C, 72.4; H, 6.9%). Since the product (A) has all hydroxyls free, no aromatic proton of ring A but all aromatic protons of ring B, and two units of 3-methylbut-2-enyl group, its structure is established as 6, 8-di-(3-methylbut-2-enyl)-kaempferol (2).

The product (B) crystallized from ethyl acetate - light petroleum mixture as yellow crystals, m.p. 304-5°; R_f 0.59 (Solvent A); green ferric reaction; n.m.r. (DMSO-d_6) δ 1.29 (s, 6H, $Me_2C<$), 1.89, 2.81 (2t, J 7Hz, 4H, Ar-CH_2-CH_2-), 6.08 (s, 1H, ArH 6), 6.90 (d, J 9Hz, 2H, ArH 3', 5') and 8.08 (d, J 9Hz, 2H, ArH 2', 6') (Found : C, 68.1; H, 5.4. Calculated for $C_{20}H_{18}O_6$; C, 67.8; H, 5.1%). With 2 moles of dimethyl sulphate it formed dimethyl ether which crystallized from MeOH as yellow flakes, m.p. 193-94°; R_f 0.81 (Solvent C); green ferric reaction; λmax 272 and 330 nm (logϵ 4.41 and 4.24 respectively); n.m.r. δ 1.41 (s, 6H, $Me_2C<$), 1.91, 2.91 (2t, J 7Hz, 4H, Ar-CH_2-CH_2-), 3.89 (s, 6H, 2MeO), 6.24 (s, 1H, ArH 6), 7.02 (d, J 9Hz, 2H, ArH 3', 5') and 8.08 (d, J 9Hz, 2H, ArH 2', 6') (Found : C, 69.4; H, 6.2. $C_{22}H_{22}O_6$ requires C, 69.1; H, 5.8%). Since these data show three hydroxyls free and one dihydropyrano unit, the product B is dihydro-2,2-dimethyl pyrano derivative of kaempferol. The orientation of the dihydropyrano ring was established as angular by direct comparison with the acid cyclization product of the product C. Hence the compound B is 4",5" dihydro-6",6"-dimethylpyrano (2",3" : 7,8)-kaempferol (3).

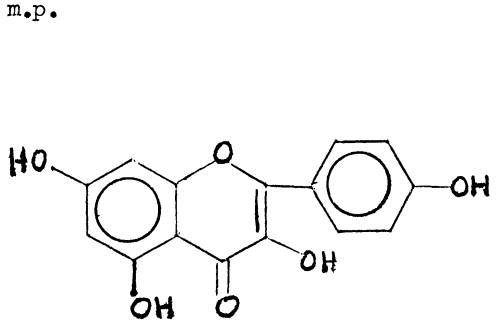
The product C crystallized from ethyl acetate-light petroleum mixture as yellow crystals, m.p. 224-225°; R_f 0.57 (Solvent D); green ferric reaction; λmax 272, 315 and 375 nm (logϵ 4.34, 4.14 and 4.21 respectively); n.m.r. (DMSO-d_6) δ 1.60, 1.72 (2s, 6H, $Me_2C=$), 3.42 (br.d, J 7Hz, 2H, Ar-CH_2), 5.20 (br.t, J 7Hz, 1H, -CH=), 6.29 (s, 1H, ArH 6), 6.92 (d, J 9Hz, 2H, ArH 3', 5') and 8.04 (d, J 9Hz, 2H, ArH 2', 6') (Found : C, 67.5; H, 5.3. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%). It formed tetraacetate as colourless needles, m.p. 170-171°; R_f 0.54 (Solvent D), λmax (EtOH) 255 and 305 nm (logϵ 4.62 and 4.55 respectively); n.m.r. δ 1.70 (s, 6H, $Me_2C=$), 2.32, 2.40 (2s, 12H, 4AcO), 3.52 (br.d, J 7Hz, 2H, Ar-CH_2), 5.16 (br.t, J 7Hz, 1H, -CH=), 6.85 (s, 1H, ArH 6), 7.24 (d, J 9Hz, 2H, ArH 3', 5') and 7.82 (d, J 9Hz, 2H, ArH 2', 6') (Found : C, 64.5; H, 5.1. $C_{28}H_{26}O_{10}$ requires C, 64.4; H, 5.02%), and tetramethyl ether as white crystals, m.p. 145°; R_f 0.57 (Solvent D); λmax 268, 300 and 345 nm (logϵ 4.49, 4.22 and 4.28 respectively); n.m.r. δ 1.70, 1.82 (2s, 6H, $Me_2C=$), 3.56 (d, J 7Hz, 2H, Ar-CH_2),

3.89, 3.96, 4.10 (3s, 12H, 4MeO), 5.21 (br.t, J 7Hz, 1H, -CH=), 6.40 (s, 1H, ArH 6), 6.98 (d, J 9Hz, 2H, ArH 3', 5'), and 8.08 (d, J 9Hz, 2H, ArH 2', 6') (Found : C, 70.6; H, 6.7. $C_{24}H_{26}O_6$ requires C, 70.2; H, 6.3%). It was further established unequivocally as 8-(3-methylbut-2-enyl)-kaempferol (4) as follows. (a) Formic acid cyclization gave only one dihydropyrano derivative (3), m.p. 304-5°, (b) Partial methylation with 3 moles of dimethyl sulphate gave trimethyl ether as yellow flakes, m.p. 175-77°; R_f 0.77 (Solvent B); λ_{max} 272 and 360 nm (logε 4.45 and 4.23 respectively); n.m.r. δ 1.70, 1.80 (2s, 6H, $Me_2C=$), 3.50 (d, J 7Hz, 2H, Ar-CH_2), 3.88 (s, 9H, 3MeO), 5.22 (t, J 7Hz, 1H, -CH=), 6.38 (s, 1H, ArH 6), 7.00 (d, J 9Hz, 2H, ArH 3', 5'), and 8.08 (d, J 9Hz, 2H, ArH 2', 6') (Found : C, 69.6; H, 5.6. Calculated for $C_{23}H_{24}O_6$: C, 69.7; H, 6.1%). Since this trimethyl ether did not undergo acid cyclization, the product (C) is 8-isopentenyl kaempferol (4). Had it been 6-isopentenyl derivative, it would have formed a dihydropyrano derivative.

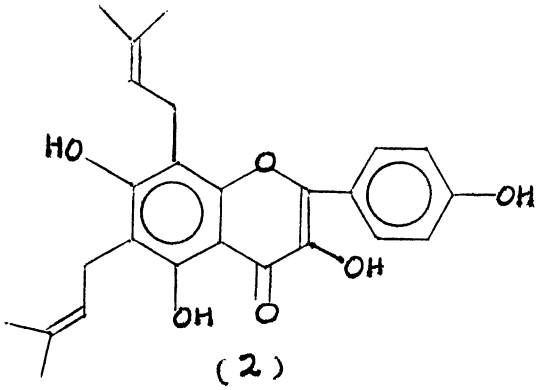
The above synthetic compound (C) was found identical with natural noranhydroicaritin (kindly supplied by Dr. Komatsu et al.) in m.p., m.m.p. and superimposable i. r. spectra. Further their tetraacetate, tri- and tetramethyl ether and dihydropyrano derivative agreed in their physical constants. Hence the present synthesis establishes unambiguously the constitution of natural noranhydroicaritin.

It has earlier been observed by Jurd [4] that polyacetate of a polyhydroxy flavonol undergoes selective displacement of 7-O-acetyl by 7-O-methyl when heated with one mole of methyl iodide in the presence of potassium carbonate and acetone. Hence synthetic noranhydroicaritin tetraacetate (5) was reacted with one mole of methyl iodide under these conditions, when 7-methoxy-3,5,4'-triacetoxy-8-(3-methylbut-2-enyl)-flavone (6) could be obtained as colourless crystals, m.p. 163°; R_f 0.58 (Solvent A); n.m.r. δ 1.72 (br.s, 6H, $Me_2C=$), 2.34, 2.44 (2s, 9H, 3AcO), 3.58 (br.d, J 6.5Hz, 2H, Ar-CH_2), 3.95 (s, 3H, MeO), 5.18 (br.t, J 7Hz, 1H, -CH=), 6.68 (s, 1H, ArH 6), 7.26 (d, J 9Hz, 2H, ArH 3', 5') and 7.86 (d, J 9Hz, 2H, ArH 2', 6') (Found : C, 65.4; H, 5.4. $C_{27}H_{26}O_9$ requires C, 65.6; H, 5.3%). The above compound on deacetylation with aqueous K_2CO_3 and crystallization of the product from ethyl acetate-light petroleum mixture yielded 8-(3-methylbut-2-enyl)-rhamnocitrin (7) as yellow crystals, m.p. 274-75°; R_f 0.60 (Solvent A); λ_{max} 273 and 378 nm (logε 4.31 and 4.18 respectively); n.m.r. (DMSO-d_6) δ 1.64, 1.78 (2s, 6H, $Me_2C=$), 3.52 (br.d, J 6Hz, 2H, Ar-CH_2), 3.90 (s, 3H, MeO), 5.28 (br.t, J 6Hz, 1H, -CH=), 6.50 (s, 1H, ArH 6), 7.00 (d, J 9Hz, 2H, ArH 3', 5') and 8.15 (d, J 9Hz, 2H, ArH 2', 6') (Found : C, 68.8; H, 5.2. $C_{21}H_{20}O_6$ requires C, 68.5; H, 5.5%). Since it has only one methoxyl group and does not undergo acid cyclization,

the presence of 7-methoxyl group is established. This compound agrees in all the properties described for the natural sample of isoanhydroicaritin (7). Further their triacetates agreed in m.p.



(1)



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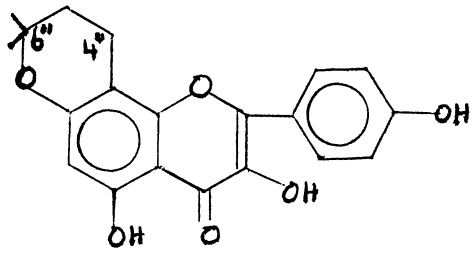

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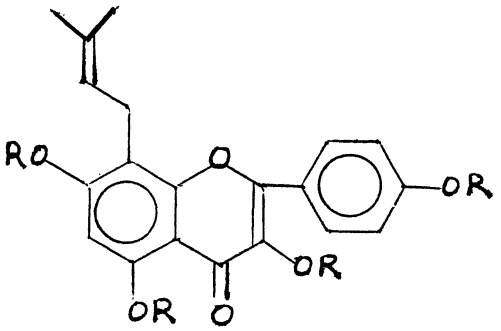
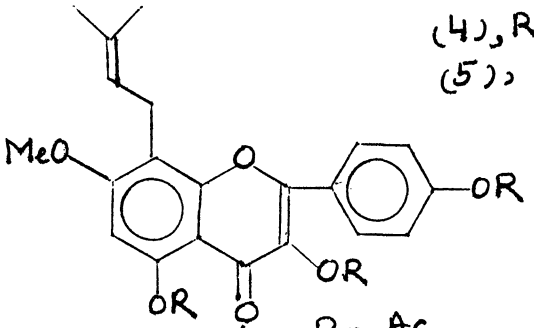


(4), R = H
(5), R = Ac



(6), R = Ac
(7), R = H

References

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2. S. Akai, M. Imaida and T. Matsukawa, J. Pharm. Soc. Japan, 55, 1139 (1935).

3. Solvents for T. L. C. are : (A) methanol : benzene (20:80); (B) ethylacetate : benzene (10:90); (C) ethylacetate : benzene (15:85); (D) methanol : benzene (25:75). Unless otherwise stated, U. V. spectra were measured in methanol and n.m.r. in $CDCl_3$ using 60 MHz n.m.r. spectrometer with TMS as internal standard.

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