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METHYLATED DERIVATIVES FROM THE HYDROLYSIS PRODUCTS OF SAFFLOMIN-A

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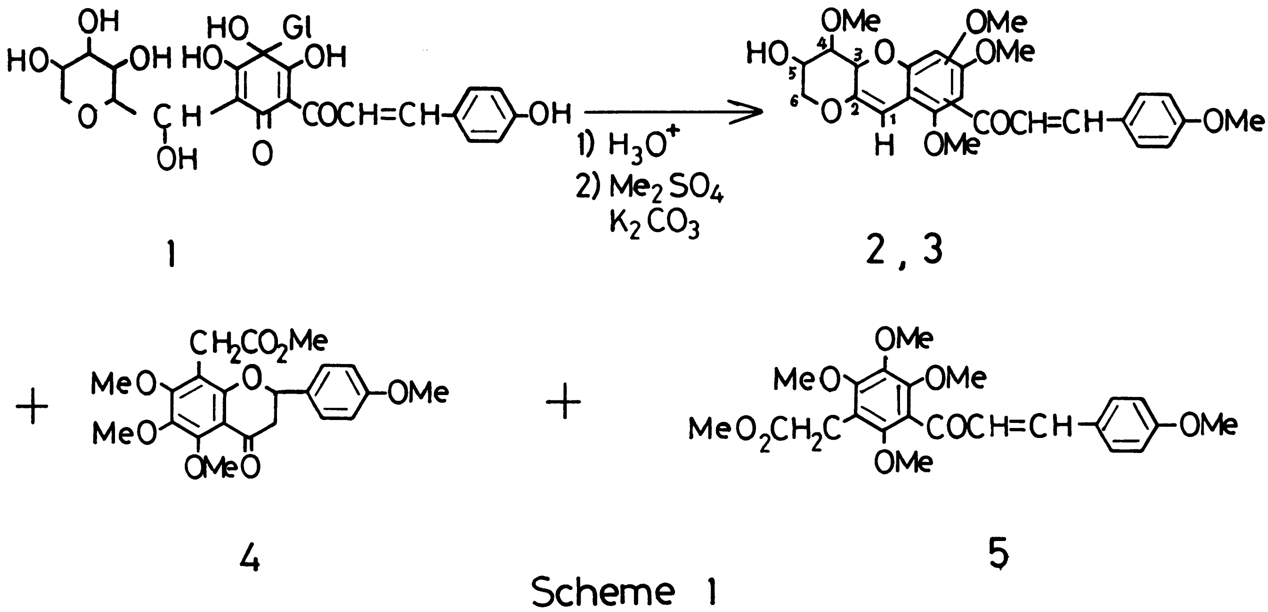
New methoxy-chalcone and flavanone derivatives were obtained by the methylation of the hydrolysis products of safflomin-A (1), a yellow component of the flowers of Safflower (Carthamus tinctorius L.). The formation of these derivatives significantly contributes to the elucidation of the structure of 1, proposed by us.

In a previous communication,[1] we have reported the investigation of the structure of safflomin-A (1), a yellow pigment of the flowers of Safflower (Carthamus tinctorius L.). Now, we wish to report the formation of the new chalcone and flavanone derivatives, two isomers of safflomidin-A pentamethyl ether dianhydrides (2 and 3),[2] 8-methoxycarbonylmethyl-4',5,6,7-tetramethoxyflavanone (4), and 3'-methoxycarbonyl-methyl-2',4,4',5',6'-pentamethoxychalcone (5), by the methylation of the hydrolysis products of 1.



Scheme 1

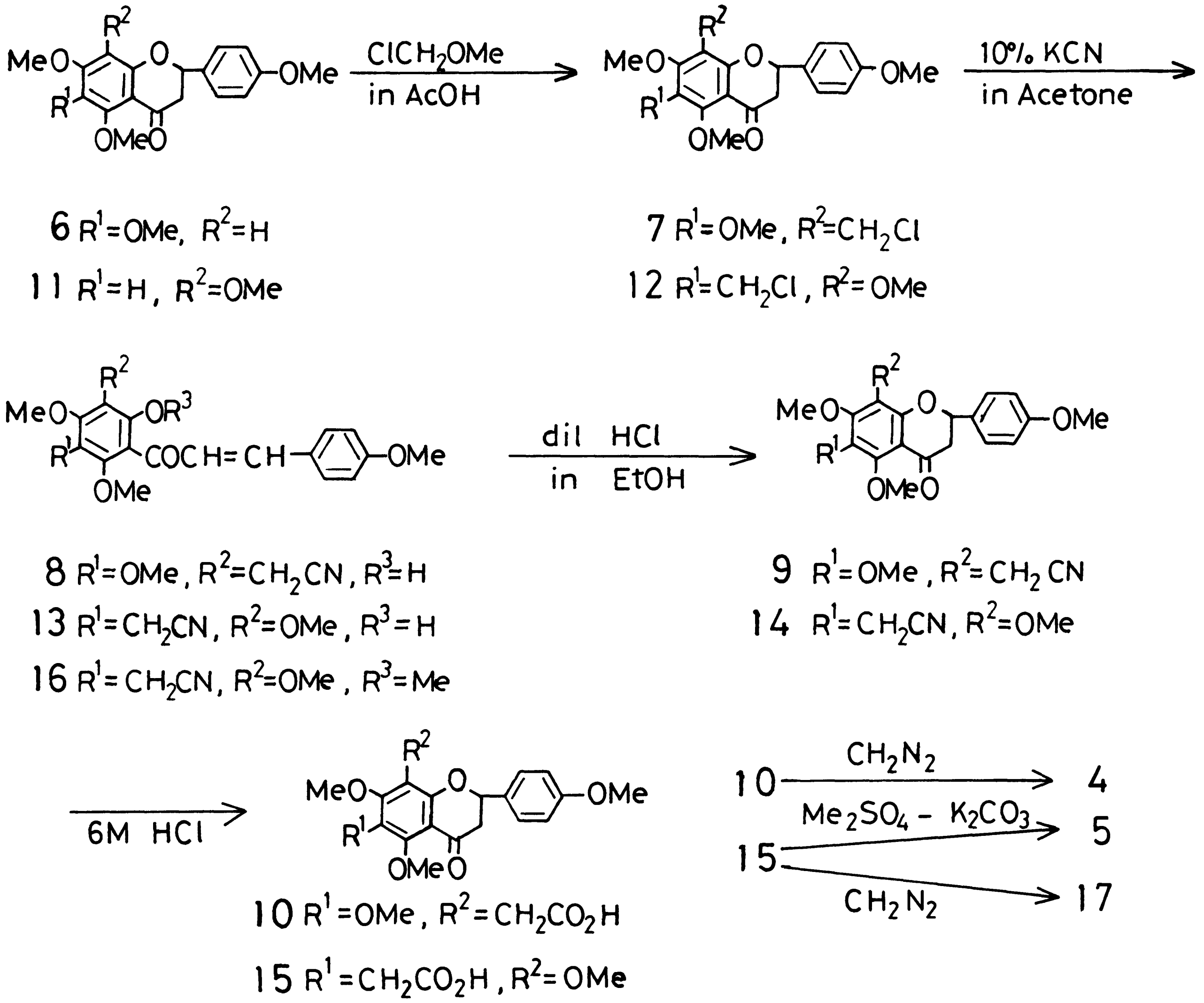
A solution of 1 in dilute methanol containing hydrochloric acid was refluxed for 18 h. Most of methanol was removed in vacuo and the resulting crude aglycon[3] was extracted with ethyl acetate to give an amorphous brownish yellow powder, which was methylated with dimethyl sulfate-potassium carbonate in acetone. The methylated products were separated by the repeated chromatography on columns of silica gel firstly with benzene-ethyl acetate (2:1) as eluent then with ether-petroleum ether (10:1) to afford four main components, A, B, C, and D.

Two isomeric structures (2 or 3) of safflomidin-A pentamethyl ether dianhydrides were respectively assigned for A and B on the basis of the following physical data.

A; mp 62-64°C, MS m/e 484 (M^+), 335, 161, and 121, UV_{max} (EtOH) 327 and 260 (sh) nm. IR (KBr) 1635 and 1593 cm^{-1} (C=O and C=C), ^{1}H-NMR ($CDCl_3$) δ 7.46 and 6.88 (each 2H, d, J=8.5Hz, p-substituted phenyl), 7.23 and 6.90 (each 1H, d, J=16.0Hz, -CH=CH-), 6.86 (1H, s, -CH=), 4.10, 3.91, 3.86, 3.81, and 3.49 (each 3H, 3, -OMe × 5), 4.86 (1H, d, J=6.0Hz, C_3-H), 3.3-4.3 (4H, m, $C_{4,5,6}$-H).

B; mp 52-55°C, MS m/e 484 (M^+), 335, 161, and 121, UV_{max} (EtOH) 327 and 255 nm, IR (KBr) 1636 and 1593 cm^{-1} (C=O and C=C), ^{1}H-NMR ($CDCl_3$) δ 7.47 and 6.89 (each 2H, d, J=8.5Hz, p-substituted phenyl), 7.27 and 6.91 (each 1H, d, J=16.0Hz, -CH=CH-), 6.87 (1H, s, -CH=), 4.11, 3.92, 3.87, 3.82, and 3.51 (each 3H, s, -OMe × 5), 4.97 (1H, d, J=6.0Hz, C_3-H), 3.3-4.3 (4H, m, $C_{4,5,6}$-H).

In the ^{1}H-NMR spectrum of the monoacetate of A, the downfield shift of the one of the four protons at 3.3-4.3 ppm ($C_{4,5,6}$-H) into 5.3 ppm (m) shows the presence of a secondary hydroxyl group in A. Furthermore, the position of the hydroxyl group in A was established at C_5, because the above lower shifted signal at 5.3 ppm did not change when C_3-proton was irradiated. Similar structure can be also expected for compound B. The stereochemistry of these derivatives, A and B, remains undisclosed.



Scheme 2

The structures of C and D have subsequently been identified by the comparison with the synthetic samples, 4 and 5, respectively.

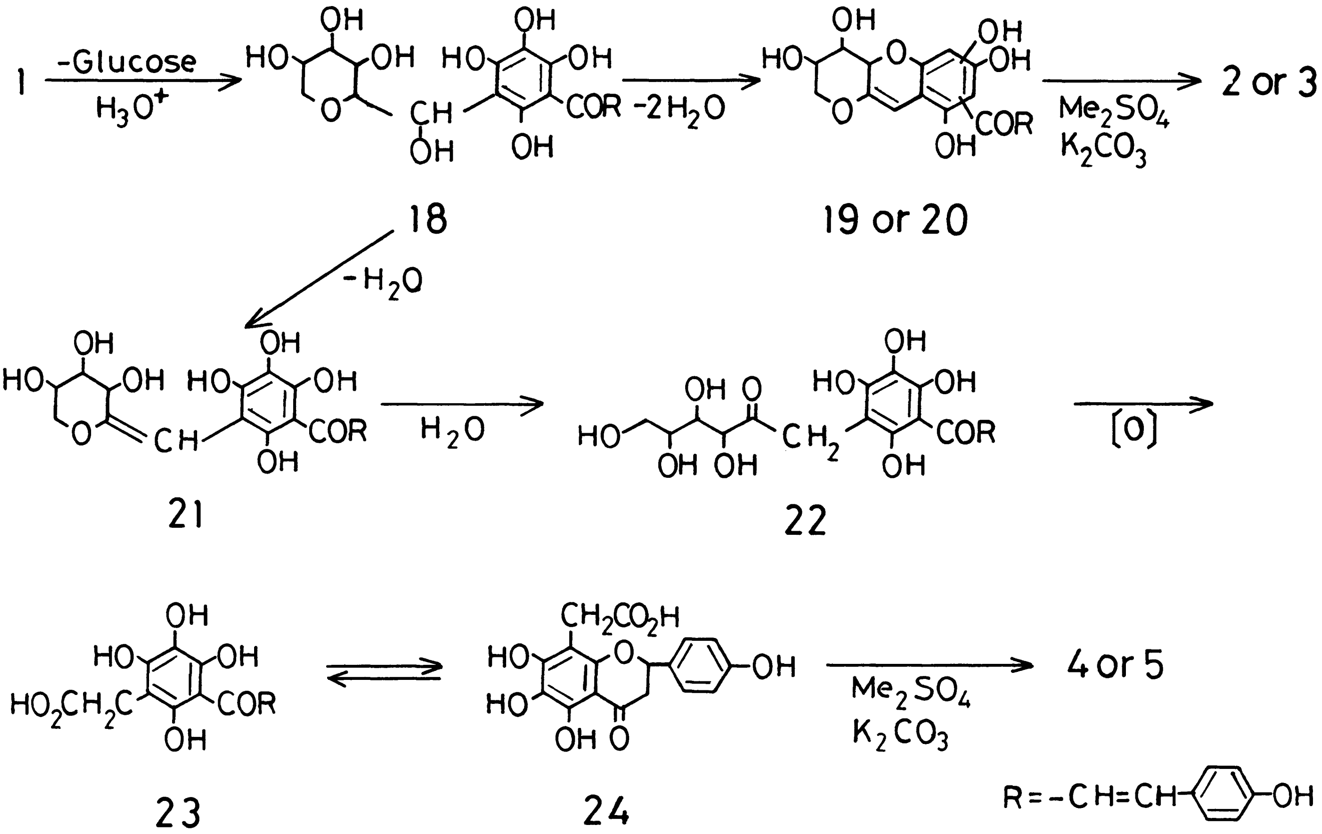
Compound C (4), mp 147-148°C, MS m/e 416 (M^+), UV $_{max}$ (EtOH) 275 and 330 nm, IR (KBr) 1735 and 1670 cm^{-1} (C=O), ^{1}H-NMR ($CDCl_3$) δ 2.77 (1H, dd, J=17.0 and 4.4Hz, C_3-H), 3.02 (1H, dd, J=17.0 and 12.0Hz, C_3-H), 3.67 (5H, s, -CH_2- and -OMe), 3.85, 3.88, 3.98, and 4.03 (each 3H, s, -OMe × 4), 5.37 (1H, dd, J=12.0 and 4.4Hz, C_2-H), 6.95 and 7.38 (each 2H, d, J=8.5Hz, p-substituted phenyl).

Compound D (5), viscous oil, MS m/e 430 (M^+), UV $_{max}$ (EtOH) 330 nm, IR ($CHCl_3$) 1730 and 1630 cm^{-1} (C=O), ^{1}H-NMR ($CDCl_3$) δ 3.66 (3H, s, -OCOMe), 3.71(2H, s, -CH_2-), 3.81, 3.83, and 3.88 (each 3H, s, -OMe × 3), 3.93 (6H, s, -OMe × 2), 6.90 and 7.40 (each 1H, d, J=16.0Hz, -CH=CH-), 6.88 and 7.50 (each 2H, d, J=8.5Hz, p-substituted phenyl).

The synthetic methods of these compounds from 6[4] or 11[4] are shown in Scheme 2.[5] Methylation of 10 with dimethyl sulfate-potassium carbonate in acetone didn't give chalcone 5. Attempt to prepare 5 from 3'-cyanomethyl-2',4,4',5',6'-pentamethoxy-chalcone (16) was also unsuccessful, because of the great difficulty of its hydrolysis.

Another flavanone isomer 17 different from 4 was obtained by the esterification of 15 with diazomethane in ether. Finally, compound 5 was obtained by the methylation of 15, prepared from 11.

The formation process of A, B, C, and D are assumed as follows (Scheme 3).



Scheme 3

Dehydration of two moles of water from the aglycon (18) give two safflomidin-A dianhydride isomers (19 and 20), which are methylated to afford 2 or 3, respectively. On the other hand, dehydration of one mole of water gives safflomidin-A monoanhydride (21), which forms carbonyl compound 22 by the addition of one mole of water. Oxidative degradation of 22 during the prolonged hydrolysis gives a mixture 23 and 24, which are methylated to afford compound 4 or 5, respectively.

The structure of safflomin-A previously proposed by us is further supported from the formation of the derivatives of the hydrolysis products described in this paper.

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References

1) J. Onodera, H. Obara, M. Osone, Y. Maruyama, and S. Sato, Chem. Lett., 1981, 433.
2) The aglycon of safflomin-A was termed safflomidin-A by us.
3) The pure aglycon of safflomin-A has not been isolated yet.
4) H. Obara, J. Onodera, and F. Yamamoto, Chem. Lett., 1973, 915; H. Obara, J. Onodera, Y. Kurihara, and F. Yamamoto, Bull. Chem. Soc. Jpn., 51, 3627 (1978).
5) The physical properties of the intermediates in the synthesis were as follows.
Compound 7; mp 140-141°C, MS m/e 392 (M^+), ^{1}H-NMR ($CDCl_3$) δ 2.78 (1H, dd, J=17.0 and 4.8Hz, C_3-H), 3.07 (1H, dd, J=17.0 and 12.0Hz, C_3-H), 3.83 (6H, s, -OMe × 2), 3.95 and 4.10 (each 3H, s, -OMe × 2), 4.68 (2H, s, $-CH_2Cl$), 5.43 (1H, dd, J=12.0 and 4.8Hz, C_2-H), 6.95 and 7.44 (each 2H, d, J=8.5Hz, p-substituted phenyl).
Compound 8; mp 123-125°C, MS m/e 383 (M^+), IR (KBr) 1624 cm^{-1} (C=O), ^{1}H-NMR ($CDCl_3$) δ 3.68 (2H, s, $-CH_2CN$), 3.83, 3.86, 3.96, and 4.13 (each 3H, s, -OMe × 4), 6.95 and 7.62 (each 2H, d, J=8.5Hz, p-substituted phenyl), 7.73 and 7.93 (each 1H, d, J=16.0 Hz, -CH=CH-), 13.63 (1H, s, -OH).
Compound 9; mp 137-138°C, MS m/e 383 (M^+), ^{1}H-NMR ($CDCl_3$) δ 2.75 (1H, dd, J=17.0 and 4.8Hz, C_3-H), 3.03 (1H, dd, J=17.0 and 12.0Hz, C_3-H), 3.62 (2H, s, $-CH_2CN$), 3.82 (6H, s, -OMe × 2), 3.93 and 4.10 (each 3H, s, -OMe × 2), 5.40 (1H, dd, J=12.0 and 4.8 Hz, C_2-H).
Compound 13; mp 135-136°C, MS m/e 383 (M^+), IR (KBr) 1623 cm^{-1} (C=O), ^{1}H-NMR ($CDCl_3$) δ 3.66 (2H, s, $-CH_2CN$), 3.76, 3.86, 3.88, and 4.17 (each 3H, s, -OMe × 4), 6.93 and 7.60 (each 2H, d, J=8.5Hz, p-substituted phenyl), 7.71 and 7.93 (each 1H, d, J=16.0 Hz, -CH=CH-).
Compound 17; oil, MS m/e 416 (M^+), UV_{max} (EtOH) 276 and 327 nm, IR ($CHCl_3$) 1736 and 1680 cm^{-1} (C=O), ^{1}H-NMR ($CDCl_3$) δ 2.75 (1H, dd, J=17.0 and 4.8Hz, C_3-H), 3.05 (1H, dd, J=17.0 and 12.0Hz, C_3-H), 3.62 (3H, s, -OCOMe), 3.69 (2H, s, $-CH_2-$), 3.78, 3.80, 3.82, and 3.98 (each 3H, s, -OMe × 4), 5.40 (1H, dd, J=12.0 and 4.8Hz, C_2-H), 6.93 and 7.39 (each 2H, d, J=8.5Hz, p-substituted phenyl).
Compound 10, 12, 14, 15, and 16 were used without purification.

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