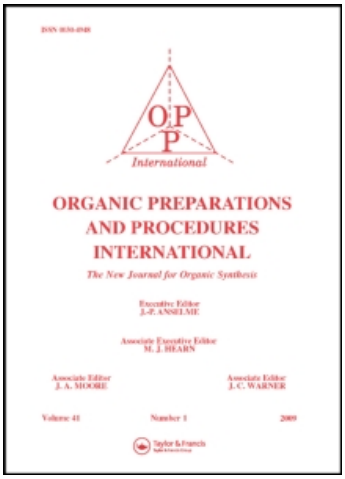

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SELECTIVE HALOGENATION OF FLAVONOLS BY HYDROHALOGENIC ACIDS IN OXIDATION SYSTEM

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SELECTIVE HALOGENATION OF FLAVONOLS BY HYDROHALOGENIC ACIDS IN OXIDATION SYSTEM

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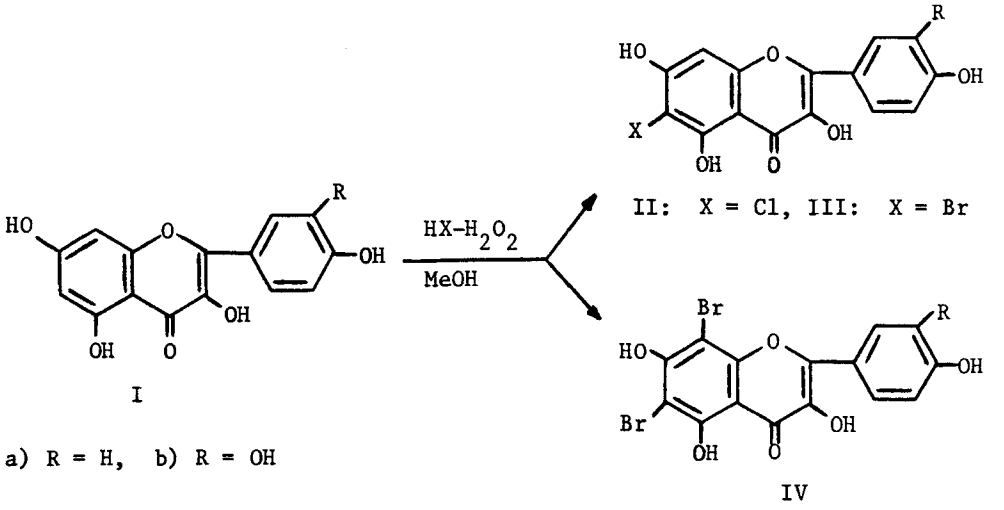
Kaemferol (Ia) and quercetin (Ib), common flavonols occurring as glycones, are widely distributed in varying concentrations in vegetables and fruits consumed by humans.[1-3] Quercetin and kaempferol are mutagenic



I

a) R = H, b) R = OH

for **Salmonella typhimurium**, [4-6] and quercetin is an intestinal, bladder and hepatic carcinogen for rats.[3,7] Sufficient quantities of quercetin, kaempferol and related analogs were required[8] to facilitate biological tests. Very little analytical work has been done concerning the replacement reaction for these compounds in acidic media. In an attempt to synthesize hydroperoxides of I in the oxidation system of hydrogen peroxide with hydrochloric acid, a convenient method for halogenation of the flavonols was discovered. The selective halogenation of position 6 of the flavonol is illustrated. Although hydrobromic acid in such an oxidation system had a marked tendency to lead to 6,8-dibromoflavonols (IVa,b), equimolar addition of hydrobromic acid below 10° resulted in 6-bromoflavonols (IIIa,b). The structural assignments for these new halogenated flavonols (II-IV) were based on their UV, NMR and MS spectra. As a typical run, the UV spectrum of IIb showed two major absorption peaks in methanol, 378 nm (band I) and 257 nm (band II), similar to those of quercetin (370 nm as band I and 255 nm as band II).[9] The NMR spectra for I were characterized by two narrow doublets at approximately δ 6.20 and 6.45 for the 6- and 8-hydrogens, respectively.[9] The NMR spectra for II and III did not display a hydrogen peak near δ 6.20, and those for 6,8-dibromoflavonols (IVa,b) displayed neither hydrogen peaks near δ 6.20 nor 6.45. Their mass spectra had the A, A+2 pattern in the correct ratio characteristic of fragments containing chlorine and bromine, respectively.

EXPERIMENTAL SECTION

All mps were uncorrected. UV spectra were measured with a Shimazu UV-240 spectrophotometer using methanol as a solvent. ^{1}H-NMR spectra were determined at 60 MHz with a JEOL PM60 NMR spectrometer with tetramethylsilane as internal references and MS were obtained on a Shimazu AUTO GCMS-6020 gas chromatograph-mass spectrometer at 70 eV using a direct inlet system. Spectral and analytical data of the flavonols (I-IV) are listed in Table 1.

TABLE 1. Spectroscopic Properties and Analytical Data for Halogenated Flavonols.

Compound	^{1}H-NMR δ in ca 5% $(CD_3)_2CO$ soln. 6-position	8-position	MS (M^+ m/e) (relative intensity)
Ia	6.23 (d, 1H, J=2.0 Hz)	6.45 (d, 1H, J=2.0 Hz)	286
Ib	6.20 (d, 1H, J=2.0 Hz)	6.45 (d, 1H, J=2.0 Hz)	302
IIa	--	6.37 (s, 1H)	320, 322 (3:1)
IIb	--	6.40 (s, 1H)	336, 338 (3:1)
IIIa	--	6.40 (s, 1H)	364, 366 (1:1)
IIIb	--	6.43 (s, 1H)	380, 382 (1:1)
IVa	--	--	442, 444, 446 (1:2:1)
IVb	--	--	458, 460, 462 (1:2:1)

Compound	Yield(%)	mp. (°C) (recryst. solvent)	Analysis(%) Calcd. (found) C	H
IIa	85	238-240 (MeOH)	50.49 (50.22)	3.64 (3.48)
IIb	90	298-300 (dil. MeOH)	48.32 (48.51)	3.42 (3.42)
IIIa	76	259-261 (MeOH)	44.89 (44.74)	3.24 (3.28)
IIIb	86	270-272 (dil. MeOH)	43.17 (43.12)	2.64 (2.71)
IVa	60	266-268 (MeOH)	40.56 (40.67)	1.80 (1.65)
IVb	60	254-255 (dil. MeOH)	39.15 (39.24)	1.74 (1.88)

Typical Procedures

1. Chlorination.- A mixture of 38% HCl (2 ml) and 30% H_2O_2 (10 ml) was added dropwise to a suspension of Ib (1 g) in redistilled methanol (MeOH) (100 ml) at 20-23° for 20 min. After being stirred for 20 hrs, the quercetin gradually dissolved. The reaction solution obtained was poured into H_2O (500 ml) to quench. The precipitate was collected by suction, washed with H_2O and dried. Recrystallization from diluted MeOH gave IIb (dihydrate), which became anhydrous at 160°/1 torr.

2. Bromination.- To a suspension of Ib (3 g) in MeOH (150 ml), 30% H_2O_2 (10 ml) was added dropwise at 0-5° and then 47% HBr (2 ml) was added dropwise for 20 min. After being stirred at 0-5° for 4 hrs, the mixture was warmed to 20° and further stirred for 1 hr, while the quercetin dissolved. The reaction solution obtained was poured into H_2O (500 ml) to quench. The precipitate was collected by suction, washed with H_2O and dried. Recrystallization from diluted MeOH gave IIIb (dihydrate), which became anhydrous at 160°/1 torr.

When double the amount of HBr was used, 6,8-dibromoquercetin (IVb) was obtained in 60% yield.

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AN IMPROVED SYNTHESIS OF WINTERS' PYRIDINE REISSERT ANALOG

Submitted by (06/02/84) John V. Cooney*, George W. Mushrush and Robert N. Hazlett

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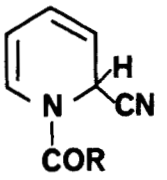
In 1974, Winters et al.[1] reported the synthesis of 1-carbethoxy-2-cyano-1,2-dihydropyridine (I). Although isolated in low (25%) yield, this compound represents the first and only known Reissert-like compound synthesized from pyridine. In contrast to quinoline, isoquinoline and



I R = OC_2H_5

II R = alkyl, aryl

related nitrogen heterocycles, pyridine has been notorious in its inability to form isolable species of structure II under conditions commonly used in