FURTHER STUDIES ON THE COLORINATION REACTION OF 7-SUBSTITUTED THEOPHYLLINE DERIVATIVES

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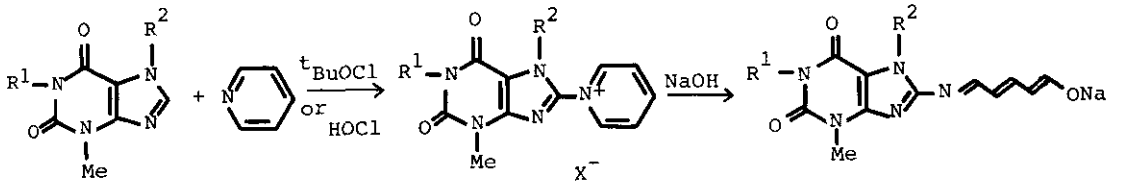
Abstract —— The colorination reaction of 7-substituted theophylline derivatives was described.

It has been well known that Bontemp's colorination reaction[1] (hypochloric acid pyridine method) is one of the most generally applicable method to detect the presence of caffeine. We have already reported[2] that the appearance of the characteristic color in the above reaction arose from the formation of the highly conjugated olefins (3a and b), via the pyridinium salts (2a and b) as outlined in Scheme 1. It is therefore of interest to investigate the application of this method to the other theophylline derivatives. We have also suggested that hypochloric acid[3] would play a role in the formation of the pyridinium salt (2a) as shown in Scheme 2, since 8-chlorocaffeine did not give the corresponding pyridinium salt in this reaction, and the reaction proceeded at near pH 5.

This reaction, however, is usually carried out in aqueous acidic solution, therefore the difficulties are mentioned to isolate the pyridinium salts formed as intermediates. Thus, we have applied this reaciton with a slight modification to 7-substituted theophylline derivatives by employing tert-butyl hypochlorite in nonaqueous solution. Treatment of caffeine (1a) with tert-butyl hypochlorite in benzene in the presence of pyridine gave rise to the corresponding pyridinium salt (2a) as a yellow powder, which was identical with the authentic specimen obtained by the known procedure. Similarly, the reaction of 7-ethyl-(1c), 7-n-propyl-(1d), and 7-allyltheophylline (1e) with tert-butyl hypochlorite in nonpolar solvent such as benzene or toluene in the presence of pyridine also afforded the pyridinium salts (2c-2e) as expected. The alkaline solution of these salts (2c-2e) exhibits characteristic absorption maxima at near 455 nm in their UV spectra, due to the



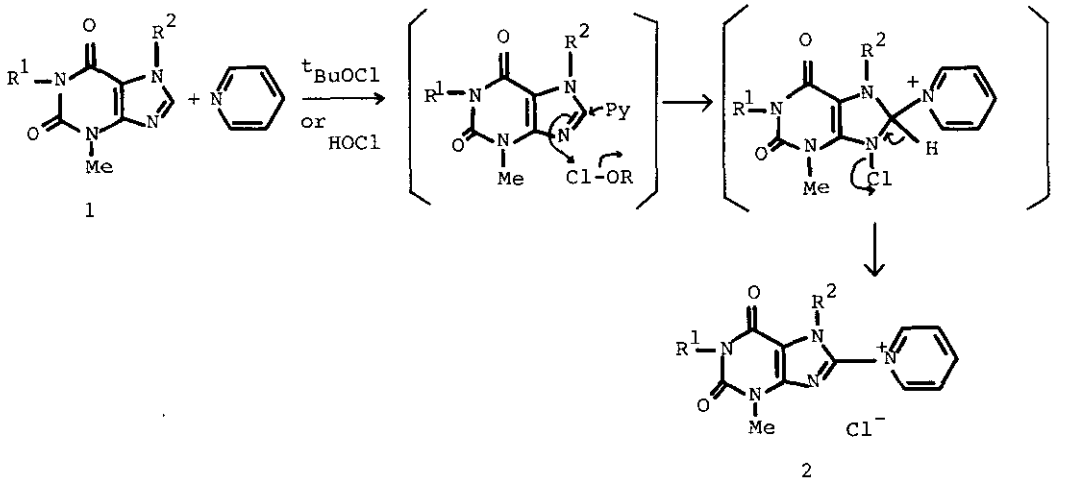
1 2 3

a : R^1=R^2=Me
b : R^1=H, R^2=Me
c : R^1=Me, R^2=Et
d : R^1=Me, R^2=n-Pr
e : R^1=Me, R^2=CH_2CH=CH_2

a : R^1=R^2=Me, X=Cl
a': R^1=R^2=Me, X=I_3
b : R^1=H, R^2=Me, X=Cl
c : R^1=Me, R^2=Et, X=Cl
c': R^1=Me, R^2=Et, X=I_3
d : R^1=Me, R^2=n-Pr, X=Cl
d': R^1=Me, R^2=n-Pr, X=I_3
e : R^1=Me, R^2=CH_2CH=CH_2, X=Cl
e': R^1=Me, R^2=CH_2CH=CH_2, X=I_3

a : R^1=R^2=Me
b : R^1=H, R^2=Me

Scheme 1



1 2

Scheme 2

presence of highly conjugated systems. These salts were further characterized as their triiodides (2a': mp 201-202°C; 2c': mp 210-212°C; 2d': mp 215-218°C; 2e': mp 185-188°C) by their microanalyses.

These results suggested that the colorination reaction mentioned above should be applicable to the other 7-substituted theophylline derivatives, and the reaction would proceed as similar to that of previously reported.[2]

EXPERIMENTAL

Melting points are not corrected. IR spectra were measured with a Hitachi 260-10 infrared spectrophotometer, UV spectra with a Hitachi 124 ultraviolet spectrometer. Mass spectra were taken with a JEOL JMS-D300 spectrometer.

N-(8-Caffeinyl)pyridinium Chloride (2a) —— To a stirred solution of caffeine (1a) (1.94g) and pyridine (0.8g) in benzene (300 ml) was added tert-butyl hypochlorite (1.5 ml) dropwise at 0°C. The stirring was continued at 0°C for 10 min and at ambient temperature for 15 min. The precipitated powder was collected by filtration, and washed with ether to give the chloride (2a) (0.2g, 6.5%); UV $\lambda_{max}^{0.1NNaOH}$: 455 nm. Since the chloride (2a) was so hygroscopic to crystallize that the further conversion of treatment with 0.1N iodine solution in water was carried out to afford the triiodide (2a') as dark reddish prisms; mp 201-202°C (Ac_2O-Et_2O); IR ν_{max}^{KBr} cm^{-1}: 1700,1660 (C=O); MS m/z: 273 (M^+), 79 (M^+-194). Anal. calcd for $C_{13}H_{14}N_5O_2I_3$:C, 23.91; H, 2.16; N, 10.92. Found: C, 24.36; H, 2.19; N, 10.70%.

N-[8-(7-Ethyltheophyllyl)]pyridinium Chloride (2c) —— To a stirred solution of 7-ethyltheophylline[4] (1c) (0.6g) and pyridine (0.6g) in dry toluene (15 ml) was added tert-butyl hypochlorite (0.9 ml) at 0°C. After stirring for 1 h at 0°C, the precipitate was collected by filtration as above to give the chloride (2c) (0.25g, 34.4%); UV $\lambda_{max}^{0.1NNaOH}$: 456 nm, which was characterized as its triiodide (2c') as dark reddish needles, mp 210-212°C (Ac_2O-Et_2O), IR ν_{max}^{KBr} cm^{-1}: 1700, 1660 (C=O). Anal. calcd for $C_{14}H_{16}N_5O_2I_3$: C, 25.20; H, 2.44; N, 10.50. Found: C, 25.76; H, 2.44; N, 10.63%.

N-[8-(7-n-Propyltheophyllyl)]pyridinium Chloride (2d) —— The reaction of 7-propyltheophylline[4] (1d) (0.6g) and pyridine (0.6g) in benzene (50 ml) with tert-butyl hypochlorite (1.0 ml) was carried out as above to give the chloride (2d) (0.15g, 19.3%); UV $\lambda_{max}^{0.1NNaOH}$: 455 nm, which was converted to the triiodide (2d') as dark reddish needles, mp 215-218°C (Ac_2O-Et_2O), IR ν_{max}^{KBr} cm^{-1}: 1700, 1660 (C=O). Anal. calcd for $C_{15}H_{18}N_5O_2I_3$: C, 26.44; H, 2.66; N, 10.28. Found: C, 26.71, H, 2.66; N,

10.28. Found: C, 26.71, H, 2.66; N, 10.17%.

N-[8-(7-Allyltheophyllyl)]pyridinium Chloride (2e) —— The reaction of 7-allyltheophylline[5] (1e) (0.4g) and pyridine (0.4g) in toluene (20 ml) with tert-butyl hypochlorite (0.6 ml) as described above gave the chloride (2e) (0.04g, 6.6%) as yellowish needles; UV $\lambda_{max}^{0.1NNaOH}$: 460 nm, which was characterized as its triiodide (2e'), mp 185-188°C (Ac_2O-Et_2O); IR ν_{max}^{KBr} cm^{-1}: 1700, 1660 (C=O). Anal. calcd for $C_{15}H_{16}N_5O_2I_3$: C, 26.52; H, 2.39; N, 10.31. Found: C, 26.22; H, 2.46; N, 9.83%.

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