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Decomposition and Stabilization of Drugs. X.[1] A New Decomposition Route of Caffeine in Alkaline Solution

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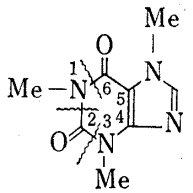
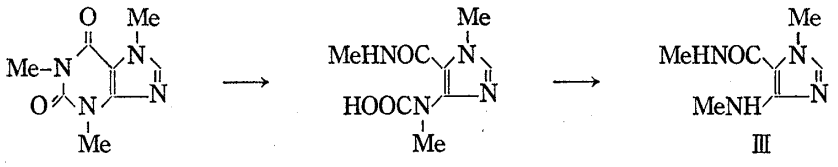
It is known that dilute sodium hydroxide solution hydrolyses caffeine (I) to caffeidine carboxylic acid (II), which is decomposed by boiling water to carbon dioxide and caffeidine (III).[3-6] This would indicate that the 1—2 bond cleavage is the only decomposition route of I. However, other routes may be assumed on the basis of the structure of I having three amide linkages at 1—6 position, 1—2 position and 2—3 position. From this point of view we attempted to clarify the decomposition route of alkaline hydrolysis of I.



I

After hydrolysis of I with 8% sodium hydroxide by heating at 70—75° for 4 hr, the reaction mixture was adjusted to pH 6.7 with concentrated hydrochloric acid. Removal of solvent gave a viscous residue, which was extracted with ethanol. Evaporation of the solvent from the extract yielded a viscous syrup, which was separated into acetone-soluble and acetone-insoluble portions, respectively. The acetone-soluble portion afforded a yellow oil, which was recrystallized from ether to give colorless prisms, mp 80—82°. It was identified as caffeidine (III)[6] by the direct comparison of infrared (IR) spectrum (KBr) and mixed melting point. On the other hand, the acetone-insoluble portion was an acid sodium salt which with an acidic resin gave the free acid (IV) (56.8%). The acid (IV) was recrystallized from ethanol–ether to give colorless needles, mp 154—156° (decomp.), while in the case of recrystallization from acetic acid-benzene, a IV-acetic acid adduct was obtained as colorless needles (mp 127—129°).[7] As the melting point of IV·HCl salt is very much different from that of II·HCl salt reported by Biltz, *et al.*,[5] the structure of IV was confirmed as follows.



I II III

Chart 1

The IR spectrum of the acidic compound (IV) showed absorption bands due to the amido group (NH) at 3325 cm^{-1}, the hydroxyl group of carboxyl group at 2600—2400 cm^{-1}, the

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6) R.H. Hoskinson, *Aust. J. Chem.*, **21**, 1913 (1968).
7) IV: mp 154—156° (decomp.), IV·HCl: mp 210—212°, II: mp 160° (decomp.), II·HCl: mp 179° (decomp.).

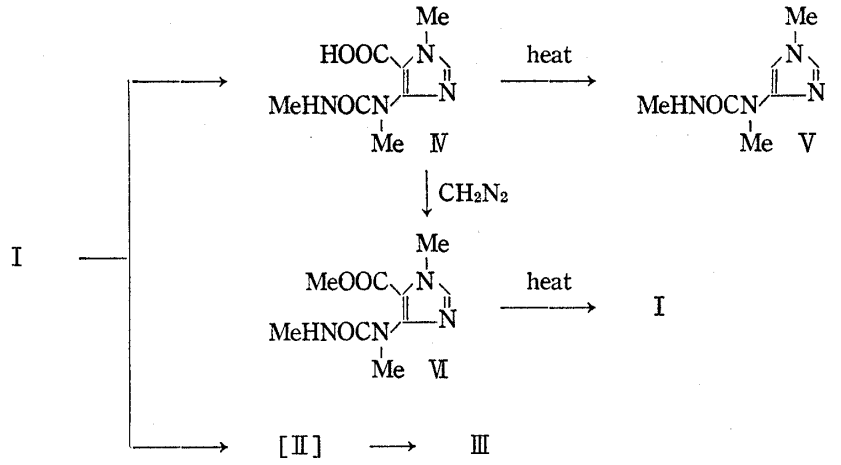


Chart 2

carboxyl group at 1700 cm^{-1} and the amido carbonyl group at 1645 cm^{-1}. The ultraviolet (UV) spectrum showed an absorption maximum at 233 nm (log ε: 3.88). The nuclear magnetic resonance (NMR) showed a doublet (3H) due to the CH_3NH at 2.80 ppm (J=4.5 Hz) and on deuteration with deuterium oxide (D_2O), the doublet at 2.80 ppm changed to a singlet. It also showed the presence of two CH_3N-groups[3.30, 4.08 ppm (each 3H, singlet)] and C-2 proton 7.72 ppm (1H, singlet) in the imidazole ring. The mass spectrum showed the parent peak at *m/e* 212 and the base peak at *m/e* 111. The elementary analysis and the mass measurement of IV established the composition $C_8H_{12}O_3N_4$. From these results, it seemed to be reasonable to assume that the structure of IV was N-[4-(5-carboxyl-1-methyimidazolyl)]-N,N'-dimethylurea (IV), and not 4-(N-carboxy-N-methyl)amino-1-methyl-5-methylaminocarbonylimidazole (II) reported by Biltz, *et al.*[5]

Further evidence for this structure was obtained by decarboxylation and methylation of IV. Decarboxylation of IV afforded a viscous oil (V), $bp_{0.3}$ 145°, which solidified on standing (mp 93—95° from ethanol–ether–petr·ether). The elementary analysis and the mass measurement of V established the composition, $C_7H_{15}ON_4$. It showed no carboxyl absorption in the IR spectrum, but displayed two signals due to the ring protons at 7.32 ppm and 6.44 ppm in the NMR spectrum indicating the existence of two aromatic protons situated at 2, and 5 position in the imidazole ring (see Experimental).

Thus, V was found to be N-[4-(1-methylimidazolyl)]-N,N'-dimethylurea as the decarboxylation product.

Furthermore, treatment of IV with diazomethane in benzene–ether furnished an monomethyl ester (VI) (mp 145—147°),[8] which showed no hydroxyl absorption in the IR spectrum and displayed a new carboxymethyl signal at 4.12 ppm in the NMR spectrum.

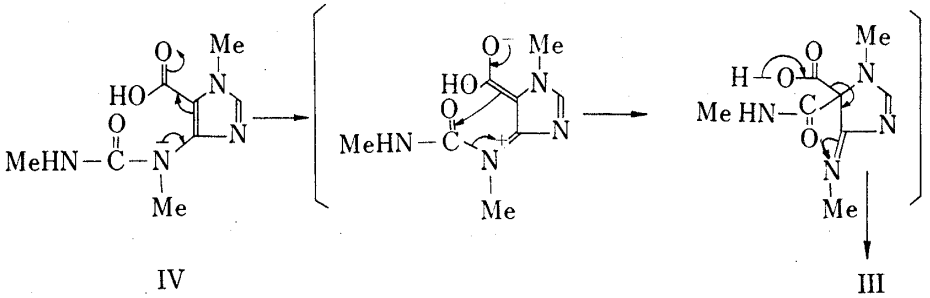


Chart 3

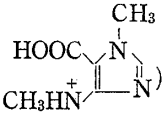
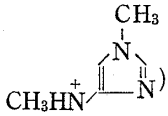
8) R. Hoskinson reported that this ester melted at 155—156°.

As the above results, it was revealed that the alkaline hydrolysis of I involves not only the 1—2 bond cleavage but also the 1—6 bond cleavage on the xanthine moiety. However, II was not isolated under this experimental condition.

Finally, IV, when heated in boiling water, yielded III (25.3%), V (56.8%) and I (5.5%).[9] A possible reaction scheme for the formation of III is shown in Chart 3.

Experimental[10]

Hydrolysis of Caffeine (I)——After a solution of I (5.0 g) in 2N NaOH (40 ml) had been kept at 70—75° for 4 hr, it was neutralized to pH 6.7 with conc. HCl. The resulting solution was evaporated to dryness *in vacuo*. The residue was extracted with EtOH. The insoluble material was removed by filtration and the filtrate was concentrated to dryness to afford a pale yellow oily residue (5.6 g). The residue was extracted with acetone. Removal of the solvent from an acetone-soluble portion yielded 1.5 g (34.6%) of III as a yellow oil. It was recrystallized from ether to give colorless prisms (III), mp 80—82°.[11] It was identified as caffeidine (III)[6] by the mixed melting point determination and IR (KBr) spectral comparison.

The acetone-insoluble portion solidified by standing to give a mass (3.8 g) as colorless powder. The aqueous solution of the above salt was passed through a column of Dowex 50W-X8 (H^+ form). The column was eluted with H_2O and the eluate was evaporated to dryness *in vacuo* to afford a colorless powder (IV) 3.1 g (58.5%), which was recrystallized from EtOH–ether to give colorless needles, mp 154—156° (decomp.). *Anal.* Calcd. for $C_8H_{12}O_3N_4$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.56; H, 5.74; N, 26.65. IR ν_{max}^{KBr} cm^{-1}: 3325 (NH), 2600—2300 (OH), 1700 (CO). UV λ_{max}^{MeOH} nm(log ε): 233 (3.88). Mass Spectrum *m/e*: 212 (M^+), 155 ($M^+-CH_3N=C=O$) (), 111 (M^+-COO; $CH_3N=C=O$) () (base peak). NMR (d_6-DMSO) ppm: 2.80 (3H, d, J=4.5 Hz, CH_3NHCON–), 3.30 (3H, s, CH_3N–CO–N–), 4.08 (3H, s, CH_3–N=), 7.72 (1H, s, C-2 aromatic proton). IV-CH_3COOH adduct: mp 127—129° (C_6H_6–CH_3COOH), colorless needles. *Anal.* Calcd. for $C_8H_{12}O_3N_4$-CH_3COOH: C, 44.11; H, 5.92; N, 20.58. Found: C, 44.34; H, 6.01; N, 20.83. IV·HCl: mp 153—155° (decomp.) (EtOH–ether, colorless needles. *Anal.* Calcd. for $C_8H_{12}O_3N_4$·HCl: C, 38.64; H, 5.27; N, 22.53. Found: C, 38.86; H, 5.46; N, 22.75.

N-[4-(1-Methylimidazolyl)]-N,N′-dimethylurea (V)——IV (3.0 g) was heated at 160—170° under a N_2 gas stream until the evolution of CO_2 gas ceased (10 min). The reddish brown oil obtained was distilled under reduced pressure to give N-[4-(1-methylimidazolyl)]-N,N′-dimethylurea (V) (1.95 g) as a yellowish viscous oil, $bp_{0.3}$ 145°, which solidified by standing. Recrystallization of the above solid from EtOH–ether–*n*-Hexane gave colorless cubics, mp 93—95°. *Anal.* Calcd. for $C_7H_{12}ON_4$: C, 49.98; H, 7.19; N, 33.31. Found: C, 50.22; H, 7.40; N, 32.82. IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1655 (CO). UV λ_{max}^{MeOH} nm(log ε): 221 (3.96). Mass Spectrum *m/e*: 168 (M^+), 111 ($M^+-CH_3N=C=O$) (base peak). NMR ($CDCl_3$) ppm: 2.83 (3H, d, J=4.5 Hz, CH_3NHCON–), 3.15 (3H, s, CH_3N–C=), 3.66 (3H, s, CH_3–N=), 6.44 (1H, d, $J_{2,5}$=1 Hz, C-5 aromatic proton), 7.32 (1H, d, $J_{2,5}$=1 Hz, C-2 aromatic proton), 8.7 (1H, br.s, NH). V·HNO_3: mp 170—172° (EtOH–ether), colorless needles. V·HCl: mp 210—212° (decomp.) (EtOH–ether, colorless cubics. V·$HClO_4$: mp 165—167° (EtOH–ether), colorless needles.

N-[4-(5-Methylcarboxyl-1-methylimidazolyl)]-N,N′-dimethylurea (VI)——To a suspension of IV (0.45 g) in C_6H_6 (40 ml) was added CH_2N_2–ether (10 ml), and it was stirred for 2 hr at room temperature. The solvent was removed *in vacuo*. The residue was recrystallized from C_6H_6–EtOH to give colorless prisms (VI), mp 145—147° (decomp.). Yield: 185 mg (38.6%). (According to the literature,[6] the above was also recrystallized from C_6H_6–ether.) This melting point was different from that of Hoskinson's sample (lit.[6] mp 155—156°). Therefore, this was recognized by elementary analysis as follows. *Anal.* Calcd. for $C_9H_{14}O_3N_4$: C, 47.78; H, 6.24; N, 24.77. Found: C, 47.61; H, 6.12; N, 24.69. IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 1705 (ester-CO), 1655, 1640 (amido-CO). UV λ_{max}^{MeOH} nm(log ε): 236 (2.97). NMR ($CDCl_3$) ppm: 2.90 (3H, d, J=4.5 Hz, CH_3NHCON–), 3.38 (3H, s, CH_3NCON–), 4.12 (6H, s, CH_3O·CO–, CH_3–N=), 7.62 (1H, s, C-2 aromatic proton). Heating of VI at 170° afforded I in quantitative yield. It was identical with an authentic sample of caffeine (I) in direct comparison of IR (KBr) and mixed melting point.

9) Neither III nor V was obtained by treatment of I under the reaction condition.

10) All melting points are uncorrected. IR spectra were obtained with a Hitachi-215 spectrophotometer and UV spectra were recorded in a Hitachi-124 spectrophotometer. NMR spectra were recorded on a JEOL, JNM-60 spectrometer. Chemical shifts of $CDCl_3$ or d_6-DMSO are reported as ppm with trimethyl silane (TMS) as an internal standard. Mass spectra were measured by the direct sample introdution technique on a Hitachi RMU-60 spectrometer.

11) lit.[6] mp 83—85°, lit.[5] mp 92—95°.

Treatment of IV in Boiling Water——A solution of IV (1.0 g) in H_2O (10 ml) was heated at 85—90° for 2 hr. The solution was evaporated *in vacuo* to give a pale yellow oily residue (0.9 g), which was subjected to column chromatography on a silicagel column. First elution with $CHCl_3$–MeOH (9: 1) gave 0.05 g of I (5.5%), second elution with $CHCl_3$–MeOH (9: 1) gave 0.45 g of V (56.8%) as a plae yellow oil. All compounds obtained here were identified by comparing their IR spectra with those of authentic samples.

Acknowledgement We thank President A. Yanagisawa and Mr. O. Takagi, Grelan Pharmaceutical Co., Ltd. for their encouragement and Dr. Shiroshi Shibuya for advice. We also thank the members of the Central Analysis Room of Pharmaceutical Institute, Tohoku University, for microanalysis.

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Studies of Oligosaccharides. XV.[1] Syntheses of Hydroquinone Glycosides of Gentio Oligosaccharides

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In the preceding papers of this series we have demonstrated the important role of sugar moieties in glycyrrhezin[3] and digitoxin[1] analogues, glycosides of pharmacological interests, as controllers of the hydrophilicity-lipophilicity balance of molecules, and also reported their effect on pharmacological activities as well as toxicities.[1] In continuation of these works this paper deals with the extension of the sugar part of arbutin by introduction of gentio oligosaccharides up to the tetraose to one of the hydroxyl groups in hydroquinone. Although the formation of the bioside from arbutin by enzymic transglycosylation was reported,[4] and the chromatographic evidences for the biosynthesis of this glycoside from hydroquinone and uridine diphosphate (UDP)-glucose are provided,[5,6] there appear to have been no papers on the chemical syntheses of this series of glycosides including the bioside.

The key intermediates of these glycoside syntheses, III and XI, were obtained by detritylation with 80% acetic acid at 70° of their precursors, II and X, respectively, which had been prepared by tritylation, followed by acetylation of I and VI, respectively.

The Königs-Knorr condensation of the intermediate III with acetobromo-glucose and -gentiobiose in the presence of silver oxide gave the acetates of the bioside and the trioside, respectively. Similarly the block condensation of XI with acetobromogentiobiose gave the acetate of the tetraoside. That the newly formed interglycosidic linkages were β was obvious from our extensive studies on the syntheses of these oligosaccharides.[7] Deacetylation of these acetates by the conventional method[8] afforded their parent glycosides, VI, IX and XIII.

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7) K. Takiura, S. Honda, T. Endo, and K. Kakehi, *Chem. Pharm. Bull.* (Tokyo), **20**, 438 (1972).
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