A FACILE CONVERSION OF THE 1-METHYL GROUP TO THE 1-AMINO GROUP OF XANTHINE DERIVATIVES

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Abstract ——— A facile conversion of the 1-methyl group to the 1-amino group of caffeine and its analogues was carried out by the reaction with hydrazine hydrate: Refluxing of caffeine(Ia) with a large amount of hydrazine hydrate(30 eq. mole) without any other solvents gave 1-amino-3,7-dimethylxanthine(IIa) in 40% yield. Similarly the reaction of 7-substituted 1,3-dimethylxanthines(Ib,Id-f) with hydrazine hydrate gave 7-substituted 1-amino-3-methylxanthines(IIb,IId-f) in 28-42% yield. Deamination of these 7-substituted 1-amino-3-methylxanthines (IIa-b, IId-f) gave the corresponding theobromine derivatives (IVa-b,IVd-f) in 90–96% yield.

It is known that xanthine derivatives have potent biological activities of phosphodiesterase inhibition and vasodilation. Recently syntheses and reactions of xanthine derivatives have been extensively investigated in connection with pentoxifylline[1] which is one of the excellent drugs acting on circulatory system. We wish to report here a facile conversion of the 1-methyl group to the 1-amino group of caffeine and its analogues, which is useful for the syntheses of new xanthine derivatives having potential phosphodiesterase inhibtion and vasodilation. Refluxing of caffeine(Ia) with a large amount of hydrazine hydrate(30 eq. mole) without any other solvents for 5 h gave 1-amino-3,7-dimethylxanthine[2](IIa) in 40% yield. In this case 40% of caffeine was recovered. Prolonged refluxing did not gain the yield, but resulted in the formation of intractable glutinous substance. Confirmation of IIa was carried out as follows: Acetylation of IIa with acetic anhydride gave diacetyl derivative(IIIa). The reductive deamination of IIa to

theobromine(IVa) was performed by the reaction with sodium nitrite in acetic acid.[3] Similar reactions of 7-substituted 1,3-dimethylxanthines(Ib-f) with hydrazine hydrate were carried out to give 7-substituted 1-amino-3-methylxanthines(Table I). Theobromine(IVa) was also aminated to IIa with hydrazine hydrate. However, in the case of theopylline(Ic) the reaction did not proceed even by refluxing for prolonged time. The deaminations of IIb and IId-f were successfully carried out (Table II). The reaction mechanism of the displacement of the methyl group by the amino group will probably be explained as depicted in the Chart 1. Initially hydrazine hydrate will attack to the electron deficient carbonyl group at 2-position of caffeine. Ring-opening followed by the elimination of methylamine and subsequent ring-closure will lead to IIa.

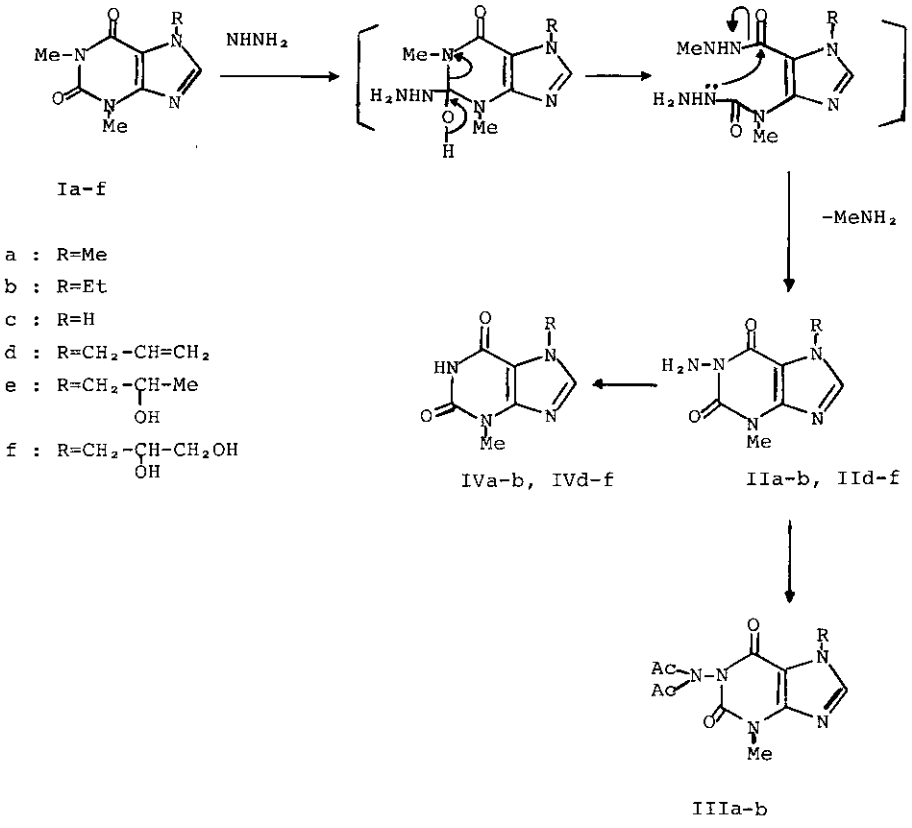

Chart 1

Table I. Yields of 7-Substituted 1-Amino-3-methylxanthines

Compd.	Mp(°C)	Reaction Time(hr)	Yield(%)
IIa	250-252	5	40
IIb	144-145	5	28
IIc		24	0
IId	129-131	5	36
IIe	180-181	5	42
IIf	183-185	5	30

Table II. Yields of 7-Substituted Theobromines

Compd.	Mp(°C)	Yield(%)
IVa[6]	> 260	96
IVb[7]	> 260	92
IVd	> 260	90
IVe[8]	> 260	91
IVf[9]	> 260	95

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