A SIMPLE SYNTHESIS OF 9-ARYLTHEOPHYLLINES AND 9-ARYL-8-AZATHEOPHYLLINES

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Treatment of 6-arylamino-1,3-dimethyluracils (I) with diazotized aniline gave 6-arylamino-1,3-dimethyl-5-phenylazouracils (II). Reductive cyclization of (II) with sodium dithionite in formic acid afforded 9-aryltheophyllines (III). Catalytic reduction of (II) with palladium charcoal and subsequent in situ treatment with sodium nitrite and hydrochloric acid yielded 9-aryl-8-azatheophyllines (IV).

Theophyllines having an aryl substituent at position 9 are of medicinal interest not only as nucleoside models of theophylline but as potential inhibitors of 3',5'-cyclic AMP phosphodiesterase.[1] However, a survey of the literature showed that the only compound known so far is 9-phenyltheophylline which was prepared in several steps beginning with 5-amino-2,4,6-trihydroxypyrimidine.[2] We now report a simple synthesis of 9-aryltheophyllines and 9-aryl-8-azatheophyllines starting with 6-arylamino-1,3-dimethyluracils (Ia-c).[3]

Treatment of the uracils (Ia-c) with diazotized aniline by the conventional method[4] gave the respective 6-arylamino-1,3-dimethyl-5-phenylazouracils (IIa-c). Refluxing the compounds (IIa-c)(0.001 mol) with sodium dithionite (0.005 mol) in formic acid (5 ml) for 3 hr, followed by concentration of the reaction mixture *in vacuo* and addition of water caused the separation of the corresponding 9-aryltheophyllines (IIIa-c). Catalytic reduction of the compounds (IIa-b)(0.001 mol) with 10% palladium charcoal (0.2 g) in ethanol (300 ml) at room temperature under atmospheric pressure and subsequent *in situ* treatment with sodium nitrite (0.003 mol) and concentrated hydrochloric acid (15 ml) at 0-5° for 3 hr yielded the desired 9-aryl-8-azatheophyllines (IVa-b), which were isolated by concentration of the reaction mixture *in vacuo* and addition of water (Scheme)(Table).[5]

Scheme

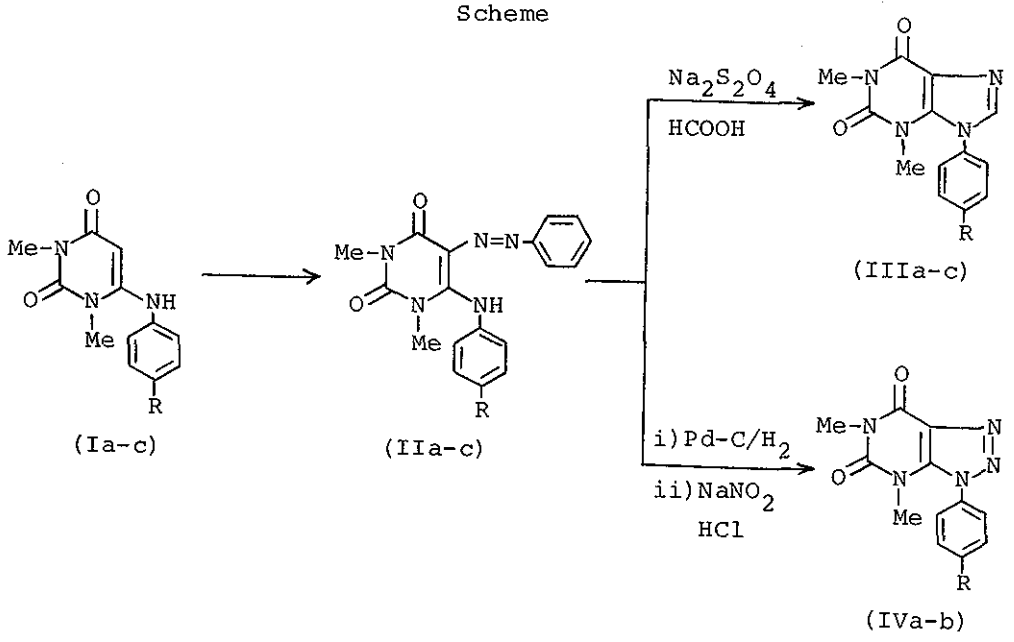

Table 9-Aryltheophyllines and 9-Aryl-8-azatheophyllines

Starting material(Mp °C; Yield %) [a]	R	Product [b]	Mp(°C)	Yield(%)
IIa (212-214; 70)	H	IIIa	>300 [c]	80
IIb (250-252; 64)	Cl	IIIb	297-298	79
IIc (233-235; 50)	Br	IIIc	296-298	79
IIa	H	IVa	195-197	50
IIb	Cl	IVb	219-220	56

a) Recrystallized from DMF.

b) Recrystallized from EtOH.

c) Lit.[2] Mp 305-307°(dec.).

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5 Satisfactory analytical and spectral data were obtained for all compounds.

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