

## 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.<sup>1)</sup> 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.<sup>2)</sup> We now report a simple synthesis of 9-aryltheophyllines and 9-aryl-8-azatheophyllines starting with 6-arylamino-1,3-dimethyluracils (Ia-c).<sup>3)</sup>

Treatment of the uracils (Ia-c) with diazotized aniline by the conventional method<sup>4)</sup> gave the respective 6-aryl-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).<sup>5)</sup>

Scheme

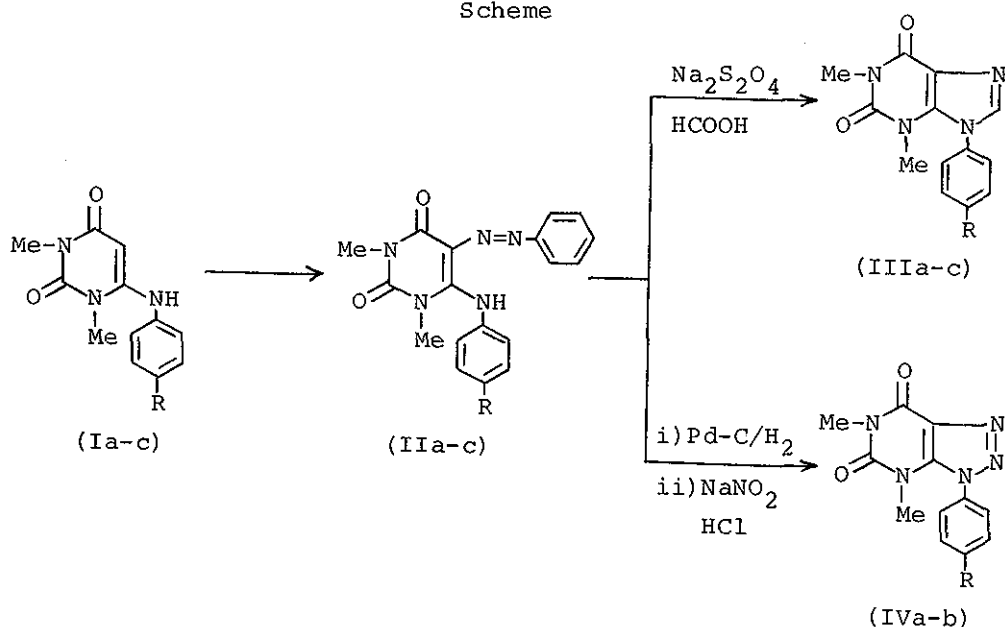


Table 9-Aryltheophyllines and 9-Aryl-8-azatheophyllines

| Starting material (Mp °C; Yield %) <sup>a)</sup> | R  | Product <sup>b)</sup> | Mp (°C)            | Yield (%) |
|--------------------------------------------------|----|-----------------------|--------------------|-----------|
| IIa (212-214; 70)                                | H  | IIIa                  | >300 <sup>c)</sup> | 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. <sup>2)</sup> Mp 305-307° (dec.).

## REFERENCES

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

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