A NOVEL SYNTHESIS OF THEOPHYLLINE DERIVATIVES

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Abstract ——— Treatment of 6-amino-5-arylazo-1,3-dimethyluracils with ethyl propiolate gave the corresponding Michael-type adducts, 6-ethoxycarbonylvinylaminouracils, which on treatment with a mixture of hydrochloric acid and acetic acid gave rise to 8-anilinomethyltheophylline derivatives.

Reaction of 6-amino-1,3-dimethyl-5-phenylazouracil (Ia) with dimethyl acethylenedicarboxylate offers a new synthetic route to pteridine.[1] We report here a novel utilization of 6-amino-5-arylazo-1,3-dimethyluracils (I) as intermediates in the synthesis of theophylline derivatives. This theophylline synthesis involves addition of ethyl propiolate to I and subsequent acid-catalyzed cyclization accompanied by rearrangement.

Thus, refluxing of Ia (0.003 mole) with ethyl propiolate (0.006 mole) in dimethylformamide (10 ml) for 7 h, followed by concentration of the reaction mixture and addition of chilled methanol, caused the separation of the corresponding Michael-type adduct, 1,3-dimethyl-6-ethoxycarbonylvinylamino-5-phenylazouracil (IIa), in 87% yield. Similarly, the treatment of several 5-arylazouracils (Ib-f)[2] with ethyl propiolate under the same conditions gave the corresponding Michael-type adducts (IIb-f) (Table 1).

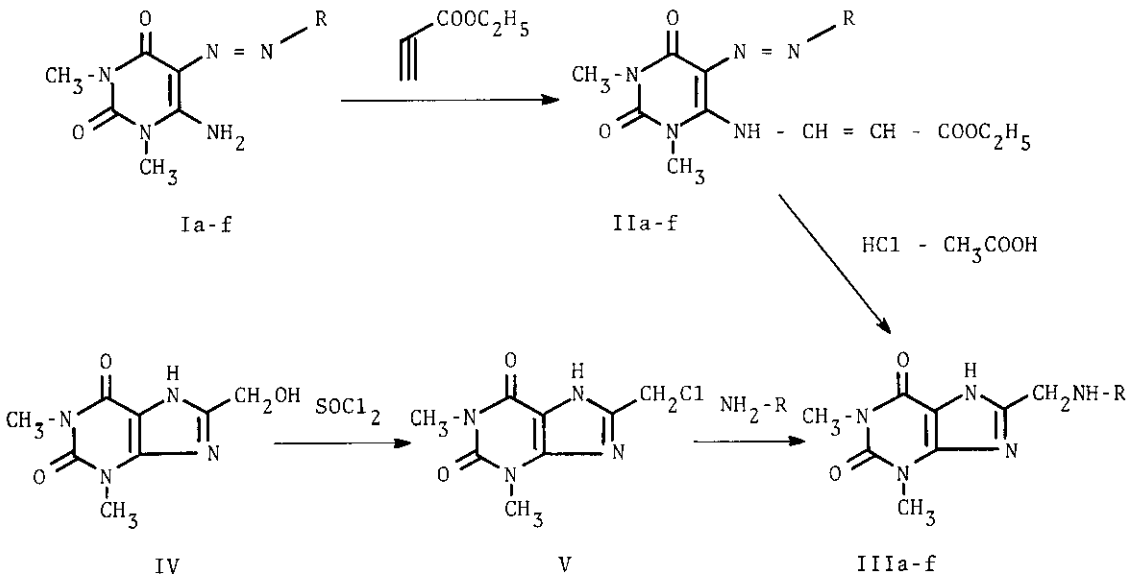
Refluxing of IIa (0.003 mole) in a mixture of concentrated hydrochloric acid and acetic acid (1:5) (10 ml) for 3 h, followed by concentration and dilution with water, gave 8-anilinomethyltheophylline hydrochloride (IIIa·HCl) in 60% yield. Treatment of IIIa·HCl with aqueous sodium hydroxide (10%) gave free 8-anilinomethyltheophylline (IIIa) in quantitative yield. The other Michael-type adducts (IIb-f)

gave 8-anilinomethyltheophylline derivatives (IIIb-f) under the same conditions (Table 2). The structures of III were assigned on the basis of elemental analyses and satisfactory spectral data, especially the presence of the benzylic protons at the 8-position in the 5.5 ppm region (in trifluoroacetic acid) in the nmr

Table 1. 5-Arylazo-1,3-dimethyl-6-ethoxycarbonylvinylaminouracils (II)

Compound No.	R	Appearance	Recrystn. solvent	Mp(°C)	Yield(%)
IIa	C_6H_5	yellow needles	ethanol	120	87
IIb	4-Br-C_6H_4	yellow needles	ethanol	139	55
IIc	4-Cl-C_6H_4	yellow needles	ethanol	141	53
IId	3-Cl-C_6H_4	yellow needles	ethanol	125	52
IIe	4-CH_3-C_6H_4	orange prisms	ethanol	121	62
IIf	3,4-$(CH_3)_2$-C_6H_3	orange prisms	ethanol	151	68

spectra. Furthermore, compounds III were identified with authentic samples prepared by the following unequivocal route. Heating 8-hydroxymethyltheophylline (IV)[3] with thionyl chloride for 1 h followed by evaporation to dryness in vacuo

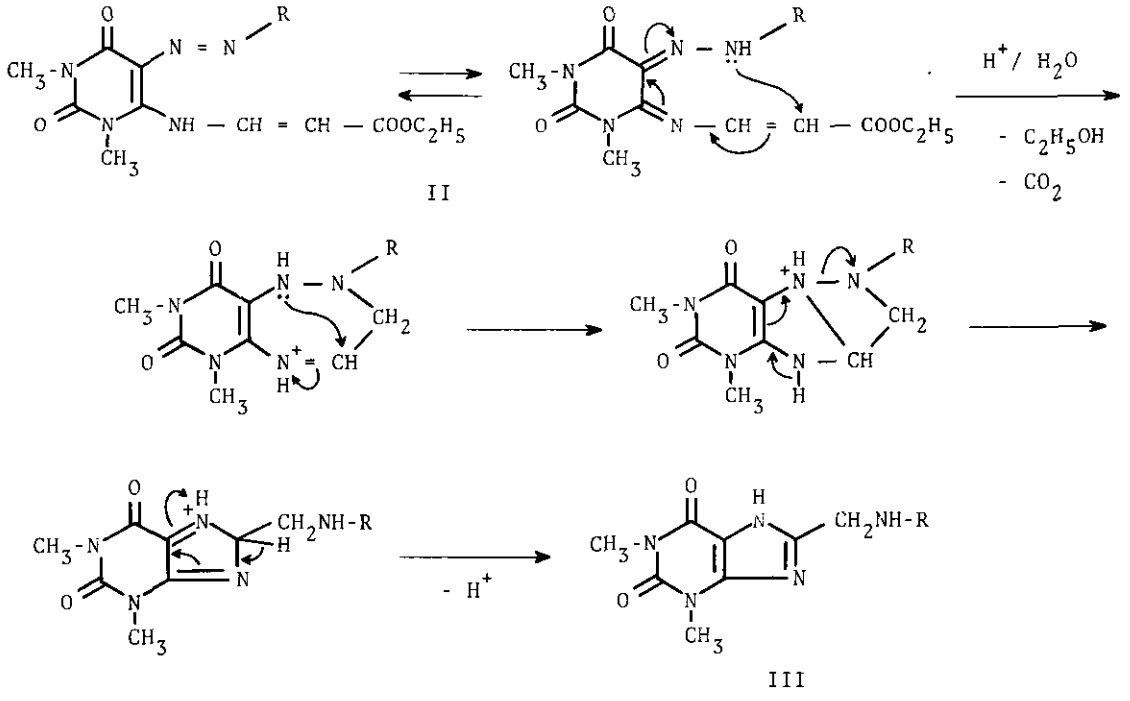


gave 8-chloromethyltheophylline (V), which without purification was treated with excess anilines at room temperature to give III.

Table 2. 8-Anilinomethyltheophyllines (III)

Compound No.	R	Appearance	Recrystn. solvent	Mp(°C)	Yield(%)
IIIa	C_6H_5	colorless powder	dimethylformamide	270	60
IIIb	4-Br-C_6H_4	colorless powder	dimethylformamide	284	46
IIIc	4-Cl-C_6H_4	colorless powder	dimethylformamide	290	51
IIId	3-Cl-C_6H_4	colorless powder	dimethylformamide	288	51
IIIe	4-CH_3-C_6H_4	colorless needles	dimethylformamide	283	63
IIIf	3,4-$(CH_3)_2$-C_6H_3	colorless needles	dimethylformamide	273	59

This novel synthesis of 8-anilinomethyltheophyllines can be rationalized in terms of the initial cyclization catalyzed by acid to a seven-membered ring (probably accompanying hydrolysis and decarboxylation). Subsequent transannular reaction



II

III

and nitrogen-nitrogen band fission followed by prototropy would give the final 8-anilinomethyltheophylline, as depicted in the above scheme.

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