A Novel Synthesis of Theophylline Derivatives

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

In the case that the arylazo group possesses an electron-releasing substituent such as methoxy, the reaction proceeded in a different way to afford 1,2-bis(theophyllin-8-yl)ethane.

The presumable reaction mechanisms for the above purine syntheses were proposed.

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5-Amino-6-arylazopyrimidines have recently been shown to be useful as the direct starting materials (without their reduction into 5,6-diaminopyrimidines) for the syntheses of purines (1), pteridines (2) and 6-azapteridines (3). In this connection, a thermal conversion of 6-alkylamino-5-phenylazouracil into a theophylline derivative was known (4). A photochemical transformation of 5-arylazo-6-dimethylaminomethyleneamino-1,3-dimethyluracils into theophylline derivatives was also known (5).

In our previous paper we have described that the treatment of 6-amino-1,3-dimethyl-5-phenylazouracil with diethyl acetylenedicarboxylate afforded 6,7-bis(methoxycarbonyl)-1,3-dimethyllumazine (6). In the present paper we report a novel utilization of 6-amino-5-arylazo-1,3-dimethyluracils (I) as intermediates in the synthesis of theophylline derivatives. This theophylline synthesis involves the addition of ethyl propiolate to I and the subsequent acid-catalyzed cyclization accompanied with rearrangement.

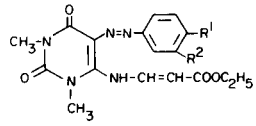
For example, the refluxing of 6-amino-1,3-dimethyl-5-phenylazouracil (Ia) with ethyl propiolate in dimethylformamide afforded a Micheal-type adduct, 1,3-dimethyl-6-ethoxycarbonylvinylamino-5-phenylazouracil (IIa). Similarly, the treatment of other 5-arylazouracils (Ib-h) with ethyl propiolate gave the corresponding Micheal-type adducts (IIb-h) (Table I). The structures of IIa-h were confirmed by the satisfactory elemental analyses and nuclear magnetic resonance data (Table II).

Next, the treatment of the Michael-type adduct IIa thus obtained with a mixture of concentrated hydrochloric acid and acetic acid (1:5) gave 8-anilinomethyltheophylline hydrochloride (IIIa•HCl). Treatment of IIIa•HCl with aqueous sodium hyroxide gave free 8-anilinomethyltheopheylline (IIIa).

In the same manner, other Michael-type adducts IIb-f were converted into the corresponding 8-anilinomethyltheophylline derivatives IIIb-f (Table III). Compounds IIIa-f showed satisfactory microanalytical data and the characteristic benzylic protons at the 8-position in the 5.5 ppm region in the nuclear magnetic resonance spectra (in trifluoroacetic acid).

Table I

5-Arylazo-1,3-dimethyl-6-ethoxycarbonylvinylaminouracils



Compound No.	R^1	R^2	Yield (%)	Mp (a) (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIa	H	H	87	120	yellow needles	$C_{17}H_{19}N_5O_4$	57.14	5.32	19.61	57.39	5.43	19.46
IIb	Cl	H	53	141	yellow needles	$C_{17}H_{18}ClN_5O_4$	52.11	4.63	17.88	52.41	4.61	17.85
IIc	H	Cl	52	125	yellow needles	$C_{17}H_{18}ClN_5O_4$	52.11	4.63	17.88	52.31	4.63	17.86
IId	Br	H	55	139	yellow needles	$C_{17}H_{18}BrN_5O_4$	46.80	4.16	16.05	46.90	4.27	16.01
IIe	CH_3	H	62	121	orange prisms	$C_{18}H_{21}N_5O_4$	58.22	5.66	18.87	58.48	5.78	18.81
IIf	CH_3	CH_3	68	151	orange prisms	$C_{19}H_{23}N_5O_4$	59.22	5.97	18.18	59.40	5.90	18.27
IIg	OCH_3	H	55	126	orange prisms	$C_{18}H_{21}N_5O_5$	55.81	5.43	18.09	55.59	5.42	17.89
IIh	OCH_3	OCH_3	57	152	orange prisms	$C_{19}H_{23}N_5O_6$	54.68	5.52	16.79	54.61	5.60	16.83

(a) All products were recrystallized from ethanol.

Scheme 1

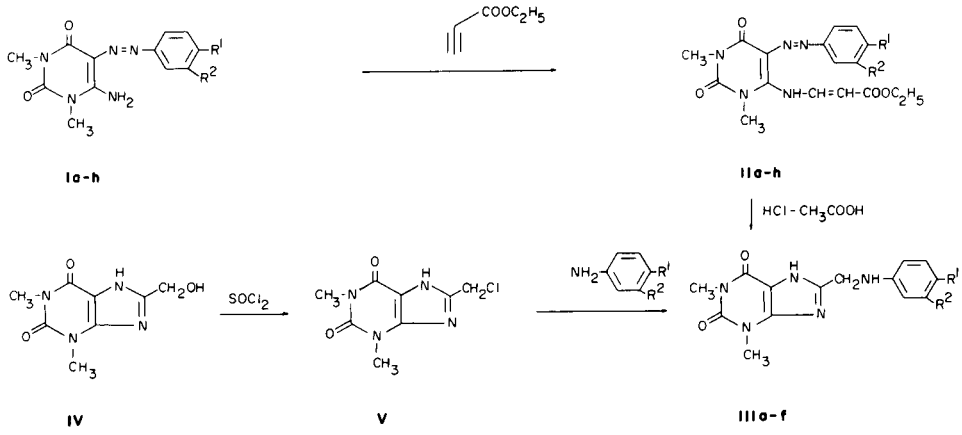


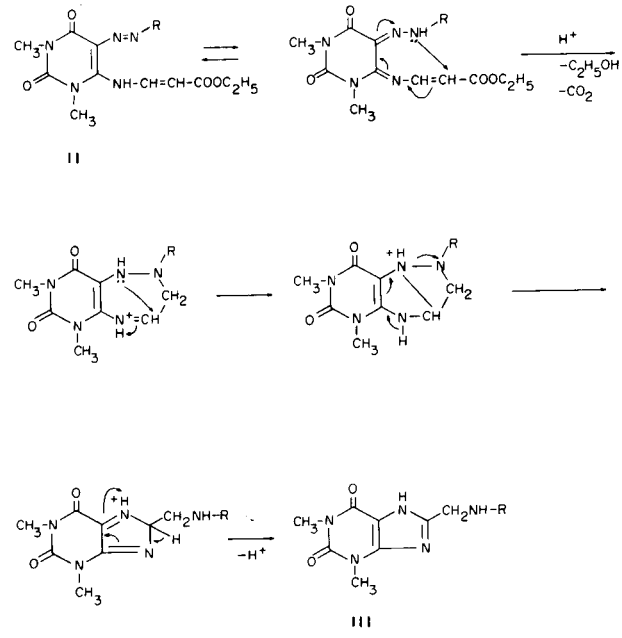
Table II

NMR Data for
5-Arylazo-1,3-dimethyl-6-ethoxycarbonylvinylaminouracils (II)

Compound No.	δ (Trifluoroacetic Acid) PPM
IIa	1.32 (3H, t, J = 7, -OCH$_2$CH_3), 3.60 (3H, s, N-CH$_3$), 3.72 (3H, s, N-CH$_3$), 4.32 (2H, q, J = 7, -OCH_2CH$_3$), 6.93-7.93 (2H, m, -CH = CH-), 7.65 (5H, s, ArH)
IIb	1.33 (3H, t, J = 7, -OCH$_2$CH_3), 3.62 (3H, s, N-CH$_3$), 3.73 (3H, s, N-CH$_3$), 4.33 (2H, q, J = 7, -OCH_2CH$_3$), 6.97-7.90 (2H, m, -CH = CH-), 7.66 (4H, s, ArH)
IIc	1.32 (3H, t, J = 7, -OCH$_2$CH_3), 3.61 (3H, s, N-CH$_3$), 3.72 (3H, s, N-CH$_3$), 4.32 (2H, q, J = 7, -OCH_2CH$_3$), 6.95-7.91 (6H, m, -CH = CH- and ArH).
IId	1.33 (3H, t, J = 7, -OCH$_2$CH_3), 3.62 (3H, s, N-CH$_3$), 3.73 (3H, s, N-CH$_3$), 4.32 (2H, q, J = 7, -OCH_2CH$_3$), 6.96-7.92 (2H, m, -CH = CH-), 7.66 (4H, s, ArH)
IIe	1.33 (3H, t, J = 7, -OCH$_2$CH_3), 2.50 (3H, s, -CH$_3$), 3.63 (3H, s, N-CH$_3$), 3.73 (3H, s, N-CH$_3$), 4.38 (2H, q, J = 7, -OCH_2CH$_3$), 7.00-7.83 (6H, m, -CH = CH- and ArH)
IIf	1.35 (3H, t, J = 7, -OCH$_2$CH_3), 2.40 (6H, s, 2 × -CH$_3$), 3.60 (3H, s, N-CH$_3$), 3.69 (3H, s, N-CH$_3$), 4.32 (2H, q, J = 7, -OCH_2CH$_3$), 6.88-7.60 (5H, m, -CH = CH- and ArH)
IIg	1.33 (3H, t, J = 7, -OCH$_2$CH_3), 3.63 (3H, s, N-CH$_3$), 3.73 (3H, s, N-CH$_3$), 4.05 (3H, s, -OCH$_3$), 4.37 (2H, q, J = 7, -OCH_2CH$_3$), 6.93-7.96 (6H, m, -CH = CH- and ArH)
IIh	1.35 (3H, t, J = 7, -OCH$_2$CH_3), 3.66 (3H, s, N-CH$_3$), 3.75 (3H, s, N-CH$_3$), 4.16 (6H, s, 2 × -OCH$_3$), 4.40 (2H, q, J = 7, -OCH_2CH$_3$), 7.00-7.65 (5H, m, -CH = CH- and ArH)

Furthermore, compounds III were identified with the authentic samples prepared by the following unequivocal route. 8-Hydroxymethyltheophylline (IV), prepared by the known procedure (7), was treated with excess thionyl chloride to give 8-chloromethyltheophylline (V). Since compound V was very unstable, without purification it was treated with anilines to give the corresponding anilinomethyltheophyllines, which were identical in all respects with the above products IIIa-f.

Scheme 2

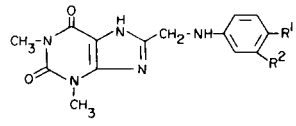


This novel synthesis of 8-anilinomethyltheophylline can be rationalized in terms of the initial cyclization catalyzed by acid to a seven-membered ring (probably accompanying hydrolysis and decarboxylation). Subsequent transannular reaction and nitrogen-nitrogen bond fission followed by prototropy would give the final 8-anilinomethyltheophylline, as depicted in Scheme 2.

In the case that the phenylazo group has an electron-releasing substituent such as methoxy, the reaction proceeded in a completely different way and 1,2-bis(theophyllin-8-yl)ethane (VI) was obtained as the sole product. Compound VI was identified with the authentic sample prepared by the known procedures (8,9).

Table III

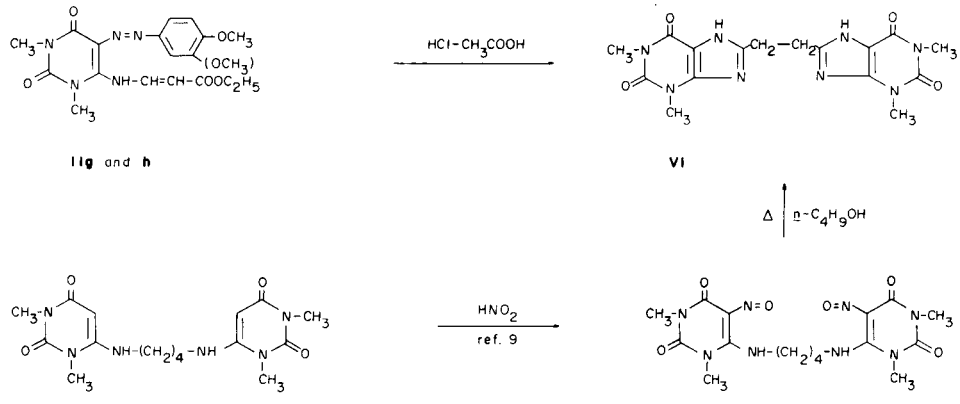
8-Anilinomethyltheophyllines



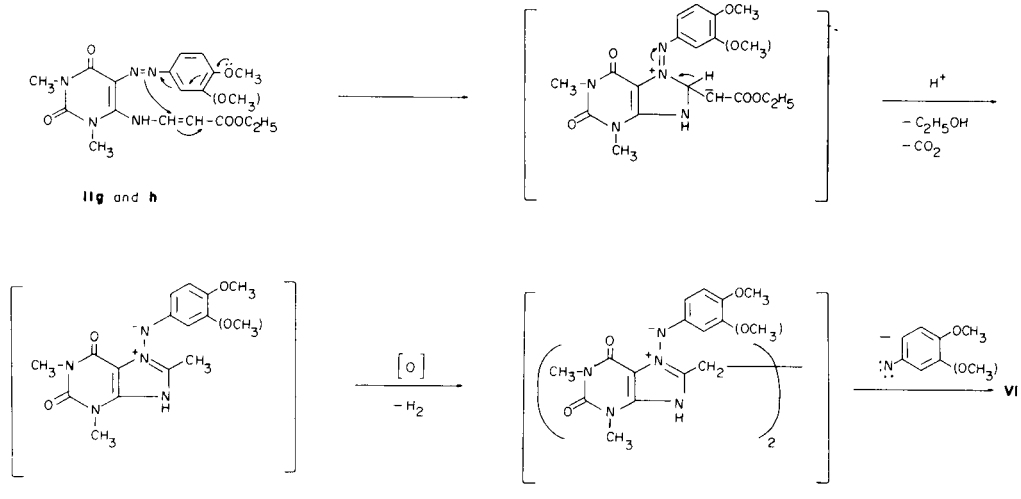
Compound No.	R^1	R^2	Yield (%)	Mp (a) (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	H	H	60	270	colorless powder	$C_{14}H_{15}N_4O_2$	58.95	5.26	24.56	58.75	5.24	24.65
IIIb	Cl	H	51	290	colorless powder	$C_{14}H_{14}ClN_5O_2$	52.59	4.38	21.91	52.86	4.25	21.72
IIIc	H	Cl	51	288	colorless powder	$C_{14}H_{14}ClN_5O_2$	52.59	4.38	21.91	52.81	4.31	21.70
IIId	Br	H	46	284	colorless powder	$C_{14}H_{14}BrN_5O_2$	46.17	3.85	19.24	46.39	3.96	19.01
IIIe	CH_3	H	63	283	colorless needles	$C_{15}H_{17}N_5O_2$	60.20	5.69	23.41	60.39	5.61	23.13
IIIf	CH_3	CH_3	59	273	colorless needles	$C_{16}H_{19}N_5O_2$	61.34	6.07	22.36	61.21	6.21	22.09

(a) All products were recrystallized from dimethylformamide.

Scheme 3



Scheme 4



The formation of compound VI can be rationalized by the initial intramolecular cyclization into the five-membered intermediate. This intermediate probably undergoes a coupling reaction by oxidation with aerial oxygen, accompanied with hydrolysis and decarboxylation. Subsequent elimination of phenylnitrene would give the final 1,2-bis(theophyllin-8-yl)ethane.

EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Identity of the compounds was confirmed by comparison of the ir spectra determined in Nujol on a JASCO IR-Al spectrometer. The nmr spectra were determined with a Hitachi R-24B spectrometer with tetramethylsilane as an internal standard.

5-Arylazo-1,3-dimethyl-6-ethoxycarbonylvinylaminouracils (Ia-h).

General Procdure.

A mixture of a 6-amino-5-arylazo-1,3-dimethyluracil (0.003 mole) and ethyl propiolate (0.006 mole) in dimethylformamide (10 ml) was refluxed for 7 hours. The reaction mixture was evaporated *in vacuo* and the residue was diluted with a small amount of chilled methanol to cause the separation of crystals which were filtered off. Recrystallization from ethanol gave the corresponding 5-arylaza-1,3-dimethyl-6-ethoxycarbonyl-vinylaminouracil (Table I).

8-Anilinomethyltheophyllines (IIa-f).

General Procedure.

5-Arylazo-1,3-dimethyl-6-ethoxycarbonylvinylaminouracil (0.003 mole) was dissolved in a mixture of concentrated hydrochloric acid and acetic acid (1:5) (10 ml) and the solution was refluxed for 3 hours. The reaction mixture was evaporated *in vacuo* and the residue was diluted with water. The anilinomethyltheophylline hydrochloride thus separated was filtered off and treated with aqueous sodium hydroxide (10%) to precipitate free 8-anilinomethyltheophylline, which was filtered off, washed with water and dried. Recrystallization from DMF gave an 8-anilinomethyltheophylline (Table III).

Alternative Synthesis of 8-Anilinomethyltheophylline (IIa).

8-Hydroxymethyltheophylline (1.0 g, 0.0048 mole) was added to excess thionyl chloride (2.86 g, 0.024 mole) and the mixture was refluxed for 1 hour. After the excess thionyl chloride was evaporated *in vacuo*, the residue was treated with excess aniline (2.0 g, 0.022 mole) under stirring at room temperature. The reaction mixture was diluted with water to cause the separation of crystals, which were filtered off. Recrystallization from ethanol gave 8-anilinomethyltheophylline which was in all respects identical with the above product.

1,2-Bis (theophyllin-8-yl)ethane.

5-Arylazo-1,3-dimethyl-6-ethoxycarbonylvinylaminouracil (IIg and h) (0.003 mole) was added to a mixture of concentrated hydrochloric acid and acetic acid (1:5) (10 ml) and the mixture was refluxed for 3 hours. The reaction mixture was evaporated *in vacuo* and the residue was diluted with water to cause the separation of crystals, which were filtered off. Recrystallization from DMF gave 1,2-bis(theophyllin-8-yl)ethane, mp $>360°C$, yield: 36% from IIg and 15% from IIh; ms: m/e 386 (M^+).

Anal. Calcd. for $C_{16}H_{18}N_8O_4$: C, 49.74; H, 4.66; N, 29.02. Found: C, 49.89; H, 4.71; N, 28.85.

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