A Novel Synthesis of 8-Arylaminotheophyllines

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A novel synthesis of 8-arylaminotheophyllines (**8a-e**) by the reaction of 5-arylazo-6-ethoxymethyleneamino-1,3-dimethyluracils (**2a-e**) or 5-arylazo-1,3-dimethyl-6-dimethylaminomethyleneaminouracils (**3a-e**) with sodium dithionite in formic acid is described.

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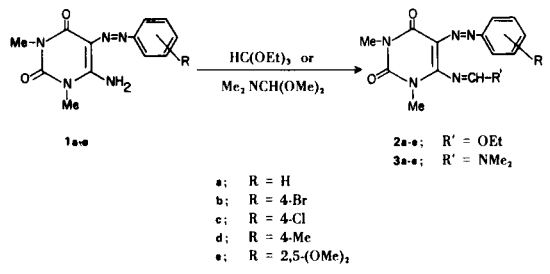
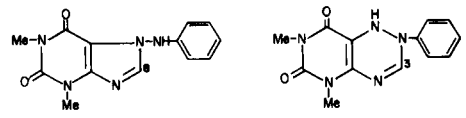
In general, 8-arylaminopurine derivatives have been synthesized by the nucleophilic displacement of the preformed 8-halogeno- or 8-alkylthiopurine with the respective arylamines as in the cases of other 8-aminopurine derivatives (1). We now present a novel synthesis of 8-arylaminotheophyllines (**8a-e**) consisting of the treatment of 5-arylazo-6-ethoxymethyleneamino-1,3-dimethyluracils (**2a-e**) or 5-arylazo-1,3-dimethyl-6-dimethylaminomethyleneaminouracils (**3a-e**) with sodium dithionite in formic acid (2).

The requisite key intermediates, **2a-e** and **3a-e**, were prepared by refluxing the appropriate 6-amino-5-arylazo-1,3-dimethyluracils (**1a-e**) with a mixture of triethyl orthoformate and dimethylformamide or with dimethylformamide dimethylacetal, respectively (Scheme I) (Table I).

Treatment of the uracil **2a** with excess sodium dithionite in formic acid at 95° for 5 minutes afforded a good yield of 8-anilinotheophylline **8a**, which was isolated by concentration of the reaction mixture *in vacuo* and addition of hot water. In this reaction, a small amount of theophylline (**9**) (3) could also be obtained by extraction of the filtrate with chloroform (4) (Method A). The structure of **8a** was initially thought as the isomeric 7-anilinotheophylline (**11**) or 5,7-dimethyl-2-phenylpyrimido-[4,5-*e*]-*as*-triazine-6,8(5*H*,7*H*)dione (**12**) (5); however, the possibilities of the structures both **11** and **12** were readily excluded since no aromatic proton at the position 8 of **11** or the position 3 of **12** could be observed in the nmr spectrum of **8a**. The characterization of **8a** was established by comparison of its ir spectrum with that of an authentic sample prepared by the conventional nucleophilic displacement of 8-chlorotheophylline (**10**) (6) with

Scheme I





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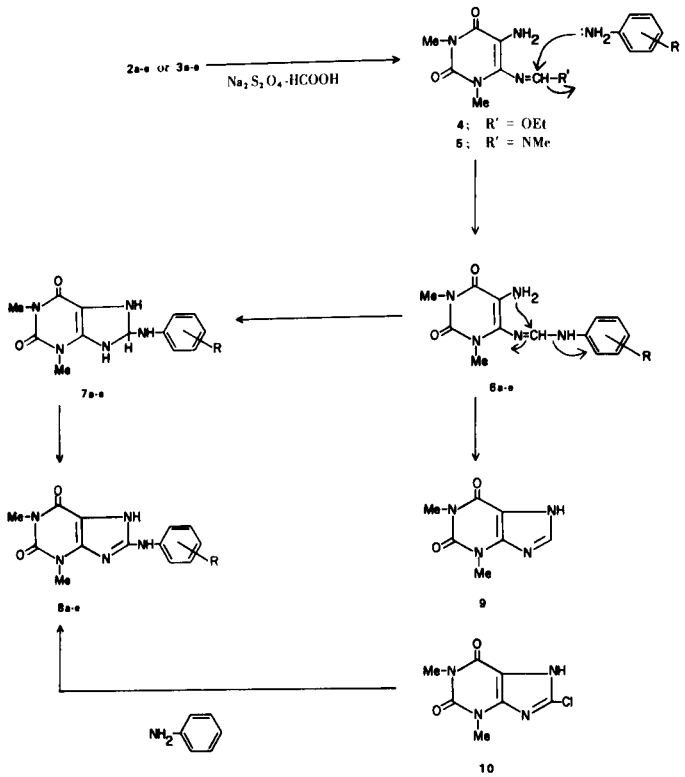
aniline at 180° for 3 hours. The reaction of other uracils **2b-e** with sodium dithionite in formic acid similarly yielded the corresponding 8-arylaminotheophyllines **8b-e** and **9**, respectively. In complete analogy with the above results, treatment of the uracils **3a-e** with excess sodium dithionite in formic acid under the same conditions provided **8a-e** and **9** in similar yields, respectively (Method B). Thes results are summarized in Table I. The exclusive formation of **8** from **2** as well as from **3** is of great interest since the analogous reaction on 4,6-diamino-5-phenylazo-2-phenylpyrimidine in a mixture of triethyl orthoformate

Scheme II

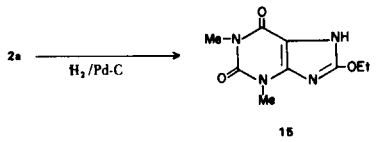


and dimethylformamide using hydrogen sulfide has been shown to give only 2-phenyladenine (7).

We suggest that this novel 8-arylaminotheophylline synthesis presumably involves the initial formation of the 5-aminouracil (**4** or **5**) by the reductive cleavage of the arylazo group of **2** or **3** with sodium dithionite (8), followed by the *in situ* nucleophilic displacement of the ethoxy group or the dimethylamino group with the liberated arylamine to give the intermediate (**6**). Thus formed **6** could then undergo intramolecular cyclizaiton by the nucleophilic attack of the amino group on the anil carbon to yield the dihydro 8-arylaminotheophylline (**7**). Subsequent aromatization would then provide the 8-arylaminotheophylline **8** (Scheme II). This speculation, particularly the possible involvement of the intermediacy of **6**, was supported by the following experiment.

Treatment of 6-(4-bromoanilino)methyleneamino-1,3-dimethyl-5-phenylazouracil (**13**), prepared by the reaction of **2a** with *p*-bromoaniline, with excess sodium dithionite in formic acid under the conditions stated above resulted in the isolation of **8a**, **8b**, **9**, and 6-amino-5-formylamino-1,3-dimethyluracil (**14**) (9) in 11, 53, 6, and 8% yield, respectively. The formation of **8b** indicates that this reaction involves the intermediacy of **6b**. Analogously, the formation of **8a** can be explained by assuming the intermediacy of **6a**, which is formed by the *in situ* nucleophilic displacement of the *p*-bromoanilino group of **6b** with the liberated aniline. Moreover, the successful isolation of **9** in this experiment implies that the formation of **9** from **2** or **3** would proceed by the intramolecular cyclization accompanying the loss of arylamine of the intermediate **6** rather than **4** or **5** (see Scheme II and Scheme III).

It should be emphasized that the conversion of **2** or **3** into **8** described in this study is greatly dependent on the reducing agent employed. For example, the catalytic reduction of **2a** with palladium on charcoal furnished 8-ethoxytheophylline (**15**) in 88% yield and the anticipated **8a** could not be isolated.



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EXPERIMENTAL

Melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. Ir spectra were recorded on a Japan Spectroscopic Co., Ltd. spectrophotometer, Model Ir-E from samples mulled in Nujol. The nmr spectrum was determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as the internal standard.

5-Arylazo-6-ethoxymethyleneamino-1,3-dimethyluracils (**2a-e**).

A mixture of the appropriate 6-amino-5-arylazo-1,3-dimethyluracils (**1a-e**) (0.01 mole) and triethyl orthoformate (50 ml.) in dimethylformamide (20 ml.) was refluxed for 5 hours at 180°. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized to give the corresponding pure products **2a-e** (see Table I).

5-Arylazo-1,3-dimethyl-6-dimethylaminomethyleneaminouracils (**3a-e**).

A mixture of the appropriate uracils **1a-e** (0.003 mole) and dimethylformamide dimethylacetal (3 ml.) was heated at 150° for 1 hour. The reaction mixture was evaporated *in vacuo* and the residue was recrystallized to give the corresponding pure products **3a-e** (see Table I).

Scheme III

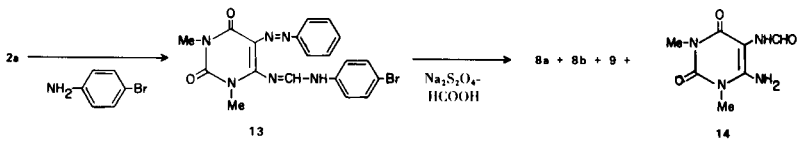

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Table I

5-Arylazo-6-ethoxymethyleneamino-1,3-dimethyluracils (**2a-e**) and 5-Arylazo-1,3-dimethyl-6-dimethylaminomethyleneaminouracils (**3a-e**)

Compound Number	M.p. (°C)	Recrystallization Solvent	Yield (%)	Calcd. (%) C	H	N	Formula	Found (%) C	H	N
2a	124-125	Ethanol	55	57.13	5.43	22.21	$C_{15}H_{17}N_5O_3$	56.89	5.43	22.40
2b	174-175	Ethanol	68	45.69	4.99	17.77	$C_{15}H_{16}BrN_5O_3$	45.72	4.95	17.75
2c	157-158	Ethanol	62	51.50	4.62	20.63	$C_{15}H_{16}ClN_5O_3$	51.65	4.63	20.47
2d	163-165	Ethanol	69	58.35	5.82	21.27	$C_{16}H_{19}N_5O_3$	58.33	5.88	21.44
2e	128-129	Ethanol	49	54.39	5.64	18.66	$C_{17}H_{21}N_5O_5$	54.09	5.60	18.94
3a	200-202	Ethanol	90	57.31	5.77	26.74	$C_{15}H_{18}N_6O_2$	57.21	5.73	26.85
3b	212-215	Ethanol-DMF	83	45.80	4.37	21.37	$C_{15}H_{17}BrN_6O_2$	45.86	4.36	21.48
3c	211-213	Ethanol-DMF	87	51.65	4.92	24.10	$C_{15}H_{17}ClN_6O_2$	51.66	4.95	24.14
3d	202-204	Ethanol	90	58.52	6.14	25.60	$C_{16}H_{20}N_6O_2$	58.54	6.12	25.73
3e	185-186	Ethanol-DMF	86	54.53	5.92	22.45	$C_{17}H_{22}N_6O_4$	54.33	5.89	22.46

Table II

8-Arylaminotheophyllines (**8a-e**)

Compound Number	M.p. (°C)	Recrystallization Solvent	Yield (%) (a) Method A	Yield (%) (a) Method B	Calcd. (%) C	Calcd. (%) H	Calcd. (%) N	Formula	Found (%) C	Found (%) H	Found (%) N
8a	> 300	Ethanol-DMF	77 (11)	74 (11)	57.56	4.83	25.82	$C_{13}H_{13}N_5O_2$	57.58	4.72	26.17
8b	> 300	Ethanol-DMF	63 (16)	69 (6)	44.58	3.46	20.20	$C_{13}H_{12}BrN_5O_2$	44.28	3.53	19.93
8c	> 300	Ethanol-DMF	48 (13)	85 (6)	51.06	3.96	22.91	$C_{13}H_{12}ClN_5O_2$	50.85	3.92	23.13
8d	> 300	Ethanol-DMF	56 (11)	42 (11)	58.93	5.30	24.55	$C_{14}H_{15}N_5O_2$	59.10	5.00	24.51
8e	> 300	Ethanol-DMF	66 (6)	48 (11)	54.37	5.17	21.14	$C_{15}H_{17}N_5O_4$	53.45	5.17	21.36

(a) The yield of theophylline (**9**) was indicated in the parenthesis.

8-Arylaminotheophyllines (**8a-e**) and Theophylline (**9**).

Method A.

A mixture of the appropriate **2a-e** (0.001 mole) and sodium dithionite (0.522 g., 0.003 mole) in formic acid (0.5 ml.) was heated at 95° for 5 minutes. The reaciton mixture was evaporated *in vacuo* and the residue was triturated with hot water. The separated solid was filtered and recrystallized to give the corresponding pure products **8a-e**.

Compound **8a**.

This compound had nmr (DMSO-d_6): δ 3.26 (3H, s, N-Me), 3.48 (3H, s, N-Me), 6.92-7.73 (5H, m, C_6H_5), 8.73 (1H, s, NH, exchangeable with deuterium oxide), 11.20 (1H, b, NH, exchangeable with deuterium oxide).

The filtrate was extracted with chloroform (three 10 ml. portions) and the chloroform extract was dried over sodium sulfate. Concentration of the chloroform solution and the recrystallization of the residue from ethanol afforded **9**, identical with an authentic sample (3).

Method B.

Treatment of the appropriate **3a-e** (0.001 mole) with sodium dithionite (0.522 g., 0.003 mole) in formic acid (0.5 ml.) under the same conditions described in Method A afforded the corresponding pure **8a-e** and **9** (see Table II).

6-(4-Bromoanilino)methyleneamino-1,3-dimethyl-5-phenylazouracil (**13**).

A mixture of **2a** (0.63 g., 0.002 mole) and *p*-bromoaniline (0.34 g., 0.002 mole) was heated at 180° for 5 minutes. After cooling, the reaction mixture was triturated with ethanol and the insoluble solid was filtered. Recrystallization from a mixture of ethanol and dimethylformamide gave pure **13** (0.85 g., 96%), m.p. 226-228°.

Anal. Calcd. for $C_{19}H_{17}BrN_6O_2$: C, 51.71; H, 3.89; N, 19.05. Found: C, 51.76; H, 3.92; N, 19.36.

Reaction of **13** with Sodium Dithionite in Formic Acid.

A mixture of **13** (0.44 g., 0.001 mole) and sodium dithionite (0.522 g., 0.003 mole) in formic acid (0.5 ml.) was heated at 95° for 5 minutes. The reaction mixture was evaporated *in vacuo* and the residue was triturated with a mixture of ethanol and water. The insoluble solid was filtered and recrystallized to give pure **8b** (0.18 g., 53%).

The filtrate which removed **8b** was evaporated *in vacuo* and the residue was suspended in water. The suspension was extracted with chloroform (three 3 ml. portions) and the chloroform solution was dried over sodium sulfate. Concentration of the extract *in vacuo* and recrystallization provided pure **8a** (0.04 g., 11%).

The aqueous layer which removed **8a** was concentrated *in vacuo* and the residue was covered with water. The separated solid was filtered and recrystallized from ethanol afforded pure 6-amino-5-formylamino-1,3-dimethyluracil **14** (0.01 g., 8%), m.p. 252°, identical with an authentic sample (9). Evaporation of the aqueous solution which removed **14** gave **9** (0.01 g., 6%).

8-Ethoxytheophylline (**15**).

A solution of **2a** (0.47 g., 0.0015 mole) in ethanol (200 ml.) containing 10% palladium on charcoal (0.2 g.) was hydrogenated at room temperature and atmospheric pressure. Hydrogenation was stopped when the theoretical volume (70 ml.) of hydrogen was consumed. The solution was filtered and the filtrate was

evaporated to dryness *in vacuo*. The residue was covered with a small amount of ethanol and the separated crystals were filtered. Recrystallization from ethanol afforded pure **15** (0.29 g., 88%), m.p. 253-255°.

Anal. Calcd. for $C_9H_{12}N_4O_3$: C, 48.21; H, 5.39; N, 24.99. Found: C, 47.87; H, 5,37; N, 24.74.

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(2) A part of this work has been reported in a preliminary form; K. Senga, M. Ichiba, H. Kanazawa, S. Nishigaki, M. Higuchi, and F. Yoneda, *Synthesis*, 264 (1977).

(3) H. Goldner, G. Dietz, and E. Carstens, *Ann. Chem.*, 691, 142 (1966).

(4) The use of water instead of formic acid decreased the yields of **8a** and **9**.

(5) The intramolecular cyclization of 6-ethoxymethyleneamino-1,3-dimethyl-5-phenylhydrazouracil, a possible precursor of **4**, could give either **11** or **12**.

(6) F. Cacace and R. Masironi, *Ann. Chim. (Rome)*, **47**, 366 (1957). Heating of a mixture of **10** (0.214 g., 0.001 mole) and aniline (0.28 g., 0.003 mole) at 180° for 3 hours caused the separation of **8a** (0.25 g., 93%).

(7) E. C. Taylor and R. W. Morrison, *J. Am. Chem. Soc.*, **87**, 1976 (1965).

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(9) Y. Ozaki, *Yakugaku Zasshi*, **80**, 1798 (1960).