coronary sinus blood, heart rate, and blood pressure were then measured. None of the compounds showed significant activity.

Experimental

Melting points were determined with the Thomas Hoover Capillary melting point apparatus. Infrared spectra were recorded on a Beckman IR-8 infrared spectrophotometer. Microanalyses were performed at the Microanalytical Laboratories of Abbott Laboratories, North Chicago, Illinois.

*N-(Phenylethyl)-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-purine-7-acetamide (**11**)*

To 12.0 g (0.05 mole) of theophylline-7-acetic acid were added dropwise 25 ml of thionyl chloride in the cold. The mixture was brought to room temperature and then refluxed on a water bath for 3 h. The thionyl chloride was removed by distillation under vacuum at low temperature. The residue was repeatedly washed with benzene to remove the last traces of thionyl chloride. A solution of 6.0 g (0.05 mole) β-phenylethylamine in 50 ml of benzene was added dropwise to the syrupy acid chloride in about 20 min. The mixture was stirred at room temperature for 48 h. The benzene was removed by distillation under vacuum and the residue was washed with acetone and filtered to give 7.0 g (40%) of a white crystalline compound. Two crystallizations from absolute ethanol afforded the analytically pure compound, m.p. 195°.

Anal. Calcd. for $C_{17}H_{19}N_5O_3$: C, 59.81; H, 5.60; N, 20.51; O, 14.06. Found: C, 59.73; H, 5.80; N, 20.32; O, 14.49.

*N-(3,4-Dimethoxyphenylethyl)-1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-purine-7-acetamide (**12**)*

This compound was prepared in 36% yield from the amine (**9**) by a similar method to that used to prepare **11**, m.p. 203°.

Anal. Calcd. for $C_{19}H_{23}N_5O_5$: C, 56.84; H, 5.77; N, 17.44; O, 19.92. Found: C, 56.86; H, 5.56; N, 17.50; O, 19.73.

*7-(1-Isoquinolylmethyl)-theophylline (**4**)*

A mixture of 8.5 g (0.025 mole) of amide (**10**) (not recrystallized), 25.0 g phosphorus pentoxide, and 50.0 g of phosphorus oxychloride was refluxed with stirring for 3.5 h. The reaction mixture was cooled and added to ice. The water layer was separated and was washed with benzene twice. The aqueous solution was neutralized with 25% sodium hydroxide solution and left at room temperature for 24 h. The solution was filtered to give 2.40 g (30%) of a brownish crystalline product, m.p. 195–197°. Two recrystallizations from methanol afforded the analytically pure product, m.p. 198–200°.

Anal. Calcd. for $C_{17}H_{15}N_5O_2$: C, 63.51; H, 4.70; N, 21.79; O, 9.95. Found: C, 63.81; H, 4.77; N, 21.69; O, 9.65.

*7-(3,4-Dihydro-1-isoquinolylmethyl)-theophylline (**13**)*

This compound was prepared in 35% yield from the amide (**11**) by a similar method, m.p. 215°.

Anal. Calcd. for $C_{17}H_{17}N_5O_2$: C, 63.14; H, 5.30; N, 21.66; O, 9.89. Found: C, 62.87; H, 5.49; N, 21.51; O, 9.89.

*7-(3,4-Dihydro-6,7-dimethoxy-1-isoquinolylmethyl)-theophylline (**14**)*

This compound was prepared in 70% yield from the amide (**12**) by a similar method. The compound was recrystallized from dimethyl formamide, m.p. 220–222°.

Anal. Calcd. for $C_{19}H_{21}N_5O_4$: C, 59.51; H, 5.52; N, 18.26; O, 16.69. Found: C, 59.39; H, 5.37; N, 18.36; O, 16.89.

A hydrochloride salt of **14** was prepared by passing dry HCl gas in dimethyl formamide solution of **14**. The salt was recrystallized from aqueous methanol.

Anal. Calcd. for $C_{19}H_{21}N_5O_4 \cdot HCl$: C, 54.34; H, 5.28; N, 16.68; Cl, 8.44; O, 15.24. Found: C, 54.27; H, 5.44; N, 16.55; Cl, 8.59; O, 15.30.

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8-Aryltheophyllines

D. S. BARIANA
Research Department, Abbott Laboratories Limited, Montreal, Quebec

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The synthesis of a number of 8-aryltheophyllines is described. These compounds were tested as coronary vasodilators.

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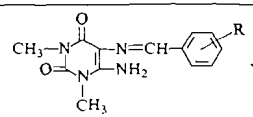
Theophylline and its 8-alkyl derivatives have been shown to possess coronary dilating effects (1). Prior to this investigation of 8-aryltheophyllines, the preparation of only a few compounds

TABLE I

6-Amino-5[(substituted-benzylidene)-amino]-1,3-dimethyluracils*

Compound number	R	Yield %	Recrystallization† solvent	Melting point (°C)	Carbon (%)		Hydrogen (%)		Nitrogen (%)	
					Calculated	Found	Calculated	Found	Calculated	Found
4	2,4-Dimethoxy	87	*a*	200–203	56.59	56.86	5.69	5.47	17.60	17.71
5	4-Diethylamino	80	*b*	235	61.98	61.87	7.03	6.92	21.26	21.09
6	2,3-Dimethoxy	80	*a*	258	56.59	56.33	5.69	5.69	17.60	17.79
7	3,4-Methylenedioxy	95	*b*	287	55.62	55.72	4.66	4.88	18.53	18.57
8	4-Isopropyl	57	*a*	210–211	63.97	63.79	6.71	6.87	18.65	18.57
9	3,4-Diethoxy	95	*b*	220	58.94	59.16	6.40	6.44	16.17	16.22
10	2,4-Dihydroxy	85	*b*	298–300	53.78	53.67	4.86	5.35	19.30	19.35
11	4-Dimethylamino	85	*b*	278	59.78	59.74	6.35	6.42	23.24	23.20
12	2,4-Dichloro	75	*b*	260–262	47.70	47.69	3.69	3.81	17.21	17.12
13	2,5-Dimethoxy	75	*a*	223	56.59	56.82	5.69	5.66	17.60	17.86
14	3-Methoxy-4-hydroxy	75	*a*	230	55.25	55.33	5.30	5.52	18.41	18.54
15	3,4-Dimethoxy	70	*a*	233	56.59	56.76	5.69	5.60	17.60	17.71
16	4-Methyl	90	*b*	270	61.74	61.86	5.92	6.21	20.57	20.56

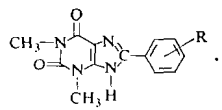
*General formula: 

†*a* = Dimethyl formamide; *b* = mixture of dimethyl formamide and methanol.

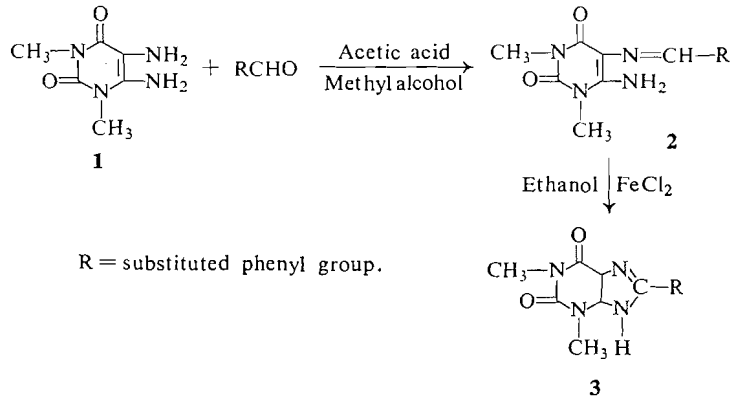
TABLE II

8-Aryltheophyllines

Compound number	R	Yield (%)	Recrystallization† solvent	Melting point (°C)	Carbon (%)		Hydrogen (%)		Nitrogen (%)	
					Calculated	Found	Calculated	Found	Calculated	Found
17	4-Diethylamino	40	*b*	290	62.36	62.44	6.46	6.44	21.39	21.51
18	2,3-Dimethoxy	60	*a*	229	56.95	57.08	5.09	5.16	17.71	17.65
19	3,4-Methylenedioxy	35	*a*	>360	56.04	56.11	4.02	4.30	18.65	18.82
20	4-Isopropoxy	30		340	64.41	64.56	6.08	6.15	18.77	18.64
21	3,4-Diethoxy	35	*a*	313	59.28	59.15	5.85	5.82	16.26	16.20
22	2,4-Dichloro	40	*a*	315	48.01	48.13	3.10	3.22	17.23	17.44

*General formula: 

†*a* = Dimethyl formamide; *b* = mixture of dimethyl formamide and methanol.



1 2 3

All the compounds were found to be inactive as vasodilators.

(2–4) had been recorded in the literature, and nothing had been published on their pharmacological activity. In order to permit a systematic evaluation of 8-aryltheophyllines as vasodilators, the present work was undertaken.

The synthesis of these compounds was carried out in two stages by known methods (2). Substituted aromatic aldehydes were condensed with 5,6-diamino-1,3-dimethyluracil (**1**) in methanolic acetic acid solution to obtain substituted benzylidinopyrimidines of the general structure **2** (Table I). The benzylidinopyrimidine intermediates on oxidation with anhydrous ferric chloride in alcohol solution gave the corresponding 8-aryltheophyllines (**3**) (Table II).

Experimental

6-Amino-1,3-dimethyl-5-benzylidinouracils

General Procedure

A solution of 5,6-diamino-1,3-dimethyluracil in methanolic acetic acid mixture (1 ml acetic acid per 5 ml methanol) was added to an equimolecular solution of an aromatic aldehyde in methanol. The mixture was allowed to stand at room temperature for 4 h. The product was filtered and recrystallized (see Table I).

8-Aryltheophyllines

General Procedure

To an alcoholic solution of 5-benzylidinopyrimidine was added a calculated amount of anhydrous ferric chloride (the ferric chloride was used mole per mole to the aromatic aldehydes used for the synthesis of respective benzylidinopyrimidines) in alcohol. A deep blue color developed. The reaction mixture was refluxed on a water bath for 4 h and allowed to stand at room temperature for 48 h. The product was filtered and recrystallized (see Table II).

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Determination of *erythro* and *threo* configurations by nuclear magnetic resonance spectroscopy

GEORGE H. SCHMID

Department of Chemistry, University of Toronto, Toronto 5, Ontario

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An examination of the nuclear magnetic resonance spectra of ten pairs of racemic *erythro* and *threo* isomers of 1,2-disubstituted-1-arylpropanes shows that the signals of the methyl protons of the *erythro* isomer always appear at lower field than the *threo* isomer. The vicinal coupling constant (J_{ab}) of the *erythro* isomer is found to be smaller than that of the *threo* isomer in six of the isomeric pairs indicating that the magnitude of J_{ab} is a poor criterion of configuration of the 1,2-disubstituted-1-arylpropanes.

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It has been shown (1, 2) that the chemical shift of a methyl group β to a phenyl ring in substituted styrene systems such as **1** depends upon the relative geometry of the two groups. Thus when the