C=O), 3100 and 3250 cm^{-1} (NH)] was prepd from **1**, $ClCH_2COCl$, and NEt_3 in PhH.

A mixt of 25 g (0.135 mole) of potassium phthalimide and 25 g (0.11 mole) of *N*-chloroacetyl-1-aminoadamantane in 100 ml of DMF was stirred at 80° for 5 hr. The mixt was distributed between $CHCl_3$ and H_2O. The $CHCl_3$ ext was washed with 0.2 *N* NaOH soln, dried (Na_2SO_4), and evapd. The residue was triturated with Et_2O to give crystals. These were filtered off to give 36.5 g (98%) of *N*-(phthalylglycyl)-1-aminoadamantane: mp 233–235°; ir (Nujol), 1655 cm^{-1} (amide C=O), 1720 and 1770 cm^{-1} (phthalimide carbonyls), 3300 cm^{-1} (NH). Recrystn (MeOH) raised the mp, 237.9–239.5°.

A mixt of 29.0 g (0.092 mole) of *N*-(phthalylglycyl)-1-aminoadamantane and 10 ml of 100% hydrazine hydrate in 200 ml of EtOH was refluxed for 2 hr. The mixt was evapd to dryness, and the residue was digested in 1200 ml of 2 *N* HCl at 50° for 10 min. The solid was removed by filtration, and the filtrate was treated with 10% NaOH soln until pptn was complete. The solid was extd with Et_2O. The Et_2O was evapd to give 18 g of residue. A 3-g portion of residue was recrystd (H_2O) to give *N*-glycyl-1-aminoadamantane, mp 131–133°. Treatment with HCl in Et_2O gave **81**.

4-(1-Adamantyl)semicarbazide (82).—A mixt of 3.54 g (0.020 mole) of 1-adamantane isocyanate[33] and 10 ml (10 g, 0.31 mole) of anhyd hydrazine in 15 ml of DMF was allowed to stand for 30 min. The mixt was poured into 100 ml of H_2O. The ppt was filtered off, washed with H_2O, and dried. Recrystn (MeCN) gave 5 g (60%) of **86**.

1-(1-Adamantyl)-3-*p*-chlorophenylurea (84).—A soln of 7.68 g (0.050 mole) of *p*-chlorophenyl isocyanate in 100 ml of Et_2O was added to a soln of 7.56 g (0.050 mole) of **1** (free base) in 300 ml of Et_2O. The mixt was stirred for 1 hr. The crystals were filtered off and recrystd (EtOH) to give 8.48 g (55%) of **84**.

***N*-(Phenylacetyl)-1-aminoadamantane (85).**—A mixt of 40 g (0.265 mole) of **1** (free base) and 150 ml (210 g, 1.28 mole) of ethyl phenylacetate was heated in a still so that the EtOH formed distd off. When the still head temp reached 98° and the pot 227°, the mixt was cooled and PhMe was added. Crystals of **85** (53 g, 74%) formed.

1-(1-Adamantyl)-2-pyrrolidinone (87).—A mixt of 43 g (0.20 mole) of 1-bromoadamantane, 62 g (0.20 mole) of Ag_2SO_4, and 60 g (0.7 mole) of pyrrolidin-2-one was stirred and heated slowly to 60°, when a rapid temp rise to 110° occurred despite water-bath cooling. After the exothermic reaction subsided, the mixt was heated at 95° for 2 hr and filtered hot, and 50 ml of H_2O was added to the filtrate. The cooled filtrate was extd with Et_2O. The ext was dried ($MgSO_4$) and evapd to give 36.0 g of crude product. Recrystn (H_2O) gave 16.3 g (37%) of **87**.

Acknowledgment.—We are indebted to Dr. R. R. Grunert, who devised and provided the mouse antiviral tests, for the biological results reported in this paper.

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Notes

8-Azatheophylline and Its Derivatives as Coronary Vasodilators[1]

D. S. BARIANA

Research Department, Abbott Laboratories Limited, Montreal, Canada

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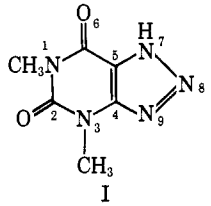
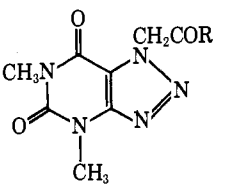
Although there is an extensive literature on theophylline, its derivatives, and water-soluble amine salts as medicinal agents, little attention has been paid to the chemistry and pharmacological effects of the 8-aza analog[2] of theophylline and its derivatives.



I

The synthesis of various derivatives and water-soluble amine salts of I for biological evaluation as coronary vasodilators was, therefore, undertaken.

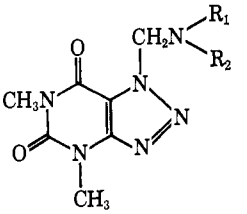
Chemistry.—The 7-acetic acid ethyl ester (II) of I was synthesized by refluxing $ClCH_2COOC_2H_5$ and I in the presence of $NaOCH_3$ according to the procedure described by Klosa[3] for the theophylline analog.



II–VIII

	R
II	OC_2H_5
III	NH_2
IV	NHC_4H_9
V	NHC_3H_7
VI	$NHCH_2CH_2OC_2H_5$
VII	$NH(CH_2)_2N(CH_3)_2$
VIII	$NH(CH_2)_3N$

Compound III was synthesized by treating $ClCH_2CONH_2$ with I in the presence of NaOH and NaI. The acid amides IV–VIII were prepared by refluxing an equimolar amount of ester II and the respective primary amines in EtOH soln for 4–6 hr. Secondary amines such as Et_2NH and *N*-phenylpiperazine did not react under these conditions. Compounds IX–XIII were obtained by treating I, a secondary amine, and 37% HCHO in EtOH soln as described previously.[4]



IX–XIII

IX	piperidine
X	morpholihe
XI	2-methylpiperidine
XII	3-methylpiperidine
XIII	4-*N*-phenylpiperazine

(1) Previous papers in this series: (a) D. S. Bariana, *Can. J. Chem.*, **46**, 3411, 3413 (1968); (b) D. S. Bariana, *J. Med. Chem.*, **12**, 927 (1969); (c) D. S. Bariana, *ibid.*, **13**, 544 (1970).

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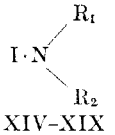
TABLE I

PHARMACOLOGICAL RESULTS

Compd	Dosage, mg/kg	pO_2 Change, %	pO_2 Duration, min	Blood pressure Change, mm	Blood pressure Duration, min	Heart rate Change, %	Heart rate Duration, min
Aminophylline[a]	2	21	28	16	10	37	10
I	10	5	40	−15	40	−3	40
II	2	10	8	−7	6	−10	6
	10	15	4	10	9	0	0
III	2	0	0	0	0	0	0
	10	19	11	−2	8	0	0
IV	2	7	15	2	10	−3	7
	10	21	60	5	5	4	5
V	2	−11	15	5	15	5	15
	10	−11	50	5	50	3	50
VI	10	18	7	−5	2	4	3
VII	2	0	0	−12	13	−3	13
	10	0	0	−7	38	−11	28
IX	2	0	0	0	0	9	19
	6.2	−20	15	−2	15	−4	15
X	2	3	12	0	0	12	12
	7	0	0	0	0	0	0
XI	2	0	0	5	5	7	13
	10	0	0	−5	10	12	40
XIII	2	26	20	25	20	14	20
	4.5	15	15	45	10	5	10
XIV	2	13	1	0	0	0	0
	3.2	100	2	37	2	19	30
XV	10	−9	5	−12	13	17	7
XVI	2	0	0	0	0	0	0
	10	0	0	−17	15	37	10
XVII	10	−3	10	−22	5	41	15
XVIII	2	0	0	10	2	12	3
	10	0	0	−30	4	−28	10
XIX	10	−21	10	−22	5	−3	10

[a] Aminophylline is an amine salt of theophylline with $H_2N(CH_2)_2NH_2$.



XIV–XIX

XIV	piperidine
XV	morpholine
XVI	ethanolamine
XVII	diethanolamine
XVIII	ethylenediamine
XIX	2-amino-1-propanol

In I, N-9 will be unreactive due to the hindrance of the *N*-3-Me group, and the investigations of previous workers[5–7] in the analogous series leaves little doubt as to the assumption that substitution occurs at N-7 and not at N-8.

Pharmacology.—Compounds I–XIX were injected in the jugular vein of anesthetized dogs at doses of 2–10 mg/kg. The change in the O_2 tension of the coronary sinus blood (pO_2), heart rate, and blood pressure were recorded as described by Schoepke, *et al.*[8] (Table I). A compound possessing good vasodilating activity should cause an increase in pO_2 for extended periods with minimal effects on heart rate and blood pressure.[9]

In the present studies, compounds which caused a 20% increase in coronary sinus blood pO_2 for at least 10 min with minimal effect on blood pressure and heart rate, qualified for further testing. Among the Mannich bases IX–XIII of I, only XIII, possessing 4-*N*-phenylpiperazine as an amine component, showed a desirable improvement on O_2 tension of the coronary sinus blood (pO_2) as compared to 8AT (I). It may be partly due to the effect of piperazine moiety in the molecule, as substituted piperazines have been shown to possess coronary vasodilating activity. The undesirable effect on blood pressure did not warrant further investigation of XIII. The amine salts XIV–XIX of I in general did not show any improvement on pO_2 increase except XIV, but the duration of increased pO_2 was too short to be of any interest. 7-Substituted ester and amide derivatives II–VII of I were the most interesting in the series. Compounds II, III, IV, and VI showed an increase in pO_2 with minor or no effect on blood pressure and heart rate. Compound IV has the most desirable activity and was further investigated. It sustained a desirable increase in pO_2 while administered iv, but was found to be inactive when administered by intrahepatic route.

TABLE II

8-AZATHEOPHYLLINE DERIVATIVES

Compd	Recrystn solvent	Yield, %	Mp, °C	Formula	Analyses
IV	H_2O	69	175–177	$C_{12}H_{18}N_6O_3$	C, H, N, O
V	MeOH–H_2O	65	202–204	$C_{11}H_{16}N_6O_3$	C, H, N, O
VI	$(CH_3)_2CO$–EtOH	33	146–149	$C_{12}H_{19}N_7O_3$	C, H, N
VII	Et_2O–Me_2CO	40	196	$C_{12}H_{18}N_6O_4$	C, H, N
VIII	Et_2O–Me_2CO	50	135	$C_{16}H_{25}N_7O_3$	C, H, N
XIV	EtOH–Et_2O	80	190–193	$C_{11}H_{18}N_6O_2$	C, H, N, O
XV	EtOH–Me_2CO	75	200	$C_{10}H_{16}N_6O_3$	C, H, N, O
XVI	EtOH–Me_2CO	80	148–150	$C_8H_{14}N_6O_3$	C, H, N, O
XVII	EtOH	75	115–118	$C_{10}H_{18}N_6O_4$	C, H, N, O
XVIII	EtOH–Me_2CO	80	255–258	$C_{14}H_{22}N_{12}O_4$	C, H, N, O
XIX	EtOH–Et_2O	75	142–145	$C_9H_{16}N_6O_3$	C, H, N, O

The amine salts XIV–XX of I were prepared by mixing an equimolar amount of I and the respective amine in MeOH soln.

The unequivocal establishment of the structures of II–XIII was attempted by various physicochemical means. Reduction of compounds IX and X did not give the desired known trialkyl-8-azatheophyllines.[5–7] The comparison of the uv spectra of IX–XII with that of 1,3,7- and 1,3,8-trimethyl analogs of I was inconclusive.[7]

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In summary, none of the compounds reported were as active as aminophylline.

Experimental Section[10]

8-Azatheophylline-7-acetic Acid Ethyl Ester (II).—To a soln of 0.69 g (0.03 mole) of Na in 50 ml of MeOH was added 5.43 g (0.03 mole) of I. The reaction mixt was refluxed for 0.5 hr and to it was added 5.0 g (0.03 mole) of $ClCH_2CO_2Et$. Refluxing was continued for 2 hr. The solvent was cooled to room temp, and the ppt was filtered and recrystd from MeOH–H_2O: yield 4.1 g (50%), mp 157–159°. *Anal.* ($C_{10}H_{13}N_5O_4$) C, H, N, O.

8-Azatheophylline-7-acetamide (III).—To a suspension of 9.2 g (0.1 mole) of chloroacetamide in 150 ml of H_2O was added 18.0 g (0.1 mole) of I, and the reaction mixt was heated to 50° for a few min. Heating was discontinued, and a soln of 4 g (0.1 mole) of NaOH and 0.1 g of NaI in 25 ml of H_2O was added. The reaction mixt was refluxed at 90° for 2 hr and cooled to room temp. The ppt was filtered and washed with cold H_2O. The product was recrystd (MeOH–DMF) to give 17.7 g (75%) of III, mp 228–230°. *Anal.* ($C_8H_{10}N_6O_3$) C, H, N.

8-Azatheophylline-7-acetamide derivatives (IV – VIII), listed in Table II, were prepd by the following procedure. A soln of 0.01 mole of II and 0.01 mole of an amine in EtOH was refluxed for 4 hr. The reaction mixt was cooled to room temp. The pptd solid was filtered and recrystd from an appropriate solvent with charcoal treatment.

8-Azatheophyllinamine salts (XIV-XIX), listed in Table II, were prepd by keeping a soln of 0.01 mole of I and 0.01 mole of an amine at room temp for 4 hr. The solvent was removed *in vacuo*, and the residue was heated with Et_2O and Me_2CO. The resultant solid was crystd from the appropriate solvent.

Acknowledgments.—The author wishes to express his appreciation to Dr. T. Darby, Mr. L. Wiemeler, and Mr. C. Shannon of the Pharmacology Department of Abbott Laboratories, North Chicago, Ill., for pharmacological investigations and permission to use their data.

(10) Melting points were determined in open capillary tubes in a Thomas-Hoover melting point apparatus. Ir spectra were determined in KBr disks with a Beckman IR-8. Microanalyses were provided by Orville Kolsto and Victor Rauschel and staff of the Abbott Microanalytical Laboratory, North Chicago, Ill.

Synthesis of 1-Amino-2-hydroxycyclopentanecarboxylic Acid

JOHN D. HUDDLE AND CHARLES G. SKINNER*

Department of Chemistry, North Texas State University, Denton, Texas 76203

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In the search for effective chemotherapeutic agents, many amino acid analogs have been synthesized in recent years; several have been found to possess antitumor properties, and others inhibit the growth of certain bacteria and viruses.[1] 1-Aminocyclopentanecarboxylic acid[2] (cycloleucine) has, for example, shown promise as a chemotherapeutic agent in the treatment of such diverse problems as acne[3] and leukemia.[4]

Few specific antimetabolites of serine and threonine are known;[1] α-methylserine inhibits the growth of *Leuconostoc mesenteroides* P-60, but other bacterial strains are unaffected; the higher homologs of threonine, 2-amino-3-hydroxypentanoic acid and 2-amino-3-hydroxyhexanoic acid, are also reported to inhibit the growth of certain bacteria. The title compound possesses a cyclopentane ring which is present in cycloleucine and also contains the combination of α-amino and β-hydroxyl groups found in serine and threonine.

Several routes for the synthesis of 1-amino-2-hydroxycyclopentanecarboxylic acid were explored, for example, ammonolysis of a halohydrin produced from 1-cyclopentenecarboxylic acid. Procedures utilizing HOCl to form a halohydrin, which had proved useful in other systems,[5,6] failed to produce the desired intermediate; however, it was obtained by the action of monochlorourea (in AcOH) on 1-cyclopentenecarboxylic acid, utilizing a procedure which had been reported for the synthesis of *trans*-2-chlorocyclopentanol.[7] Upon ammonolysis of this chlorohydrin, the only amino acid isolated was 2-amino-1-hydroxycyclopentanecarboxylic acid.[8] This result is consistent with some previous studies where it was reported that several 2-chloro-3-hydroxy-substituted acids produced the corresponding 2-hydroxy-3-amino derivatives on ammonolysis[9–11] presumably through the mediation of an epoxide intermediate.

Ultimately, the synthesis of 1-amino-2-hydroxycyclopentanecarboxylic acid was accomplished by a route similar to the method for the preparation of serine and threonine.[12,13] 1-Cyclopentenecarboxylic acid was converted into an acetoxymercurimethoxy adduct which, upon bromination, yielded 1-bromo-2-methoxycyclopentanecarboxylic acid. Ammonolysis of this material gave the corresponding aminomethoxy derivative which was finally hydrolyzed with 49% HI to produce the desired amino acid analog. The ir spectrum of this compound was consistent with that of an α-amino-β-hydroxycarboxylic acid.

The nmr spectrum of 1-amino-2-hydroxycyclopentanecarboxylic acid indicated the absorption of CH (adjacent to OH) at δ 4.54; whereas, in the spectrum of 2-amino-1-hydroxycyclopentanecarboxylic acid, the CH (adjacent to NH_2) absorbs at δ 3.80. These data are comparable to those observed using model compounds, serine and isoserine, with absorptions at δ 4.18 and 3.48, respectively, and are consistent with the greater deshielding effect expected for the more electronegative OH. The CH of 1-amino-2-methoxycyclopentanecarboxylic acid was found to absorb at δ 4.20.

Gas chromatographic analysis of the trimethylsilyl derivatives of 1-amino-2-hydroxycyclopentanecarboxylic acid indicated that these compounds are present in approximately equimolar mixtures of cis and trans isomers. This would be anticipated since the replacement of the BrHg group with Br is known to proceed with

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