

As can be seen from Table VII several compounds (IVa-DL, IVb-DL, IVb-L, and IVc-L) have noteworthy activity. Compound IVb-L is particularly interesting since it appears to be more potent than L-T<sub>3</sub>. A more detailed study of the activity in several thyromimetic assay procedures of most of the compounds listed in Table VII will be described shortly.<sup>25</sup>

(27) C. M. Greenberg, B. Blank, F. R. Pfeiffer, and J. F. Pauls, *Ann. N. Y. Acad. Sci.*, in press.

## Thyromimetics. II. The Synthesis and Hypocholesteremic Activity of Some $\beta$ -Diethylaminoethyl Esters of Iodinated Thyroalkanoic Acids

BENJAMIN BLANK, FRANCIS R. PFEIFFER, CYRUS M. GREENBERG, AND JAMES F. KERWIN

Research and Development Division, Smith Kline and French Laboratories, Philadelphia 1, Pennsylvania

Received May 4, 1963

The synthesis of a number of  $\beta$ -diethylaminoethyl esters of iodinated thyroalkanoic acids is described. The ability of these compounds to lower plasma cholesterol levels in rats fed a cholesterol-cholic acid diet is also reported. A study of the hypocholesteremic activity of the compounds tested indicates that maximum activity is found in those compounds with a two-carbon side chain and a 3'-iodine atom or isopropyl group (VII, VIII, and XIII).

Although the relationship between serum cholesterol levels and the occurrence of atherosclerosis has not been conclusively demonstrated, the implications are such that the search for hypocholesteremic agents is currently being carried out by many investigators. In the search for a useful cholesterol-lowering agent much attention has been devoted to thyromimetic agents with current interest centering on the D-isomers of thyroxine and 3,3',5-triiodothyronine and iodinated thyroacetic, -formic, and -propionic acids.<sup>1-9</sup>

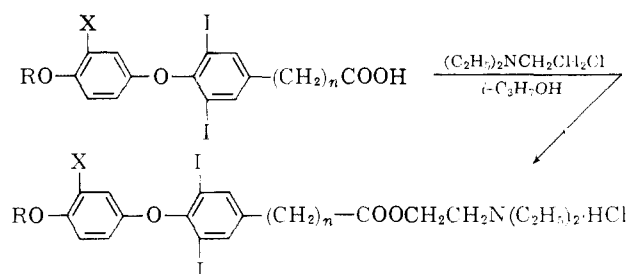
While most of these compounds have some effect on serum cholesterol levels in animals few have proved satisfactory for use in man.

In an effort to obtain agents which have a specific hypocholesteremic action with few or no side effects a series of diethylaminoethyl esters of various iodinated thyroalkanoic acids was prepared (Table I). Several 4'-methyl ethers were also prepared since it appears that these derivatives often possess a large separation between the minimum effective hypocholesteremic dose and the dose which causes weight loss in animals.<sup>7</sup> Since it had been demonstrated in our laboratories that an isopropyl group can be substituted for iodine in the 3'-position of 3,5-diiodothyronine without causing any loss in hypocholesteremic activity,<sup>10</sup> the 3'-isopropyl analog XIII of the  $\beta$ -diethylaminoethyl ester of 3,3',5-triiodothyroacetic acid (VII) was prepared to see if this relationship proved true in this series also.

To prepare the esters listed in Table I the requisite

**Acknowledgment**—We wish to express our gratitude to Mr. Roger O'Connor for technical assistance throughout this study. We also wish to thank Mrs. Doris Ralston and staff for elemental analyses and Mr. J. Walter Hamill and staff for determining optical relations.

acids were treated with  $\beta$ -diethylaminoethyl chloride in dry 2-propanol.<sup>11</sup>



R = H or CH<sub>3</sub>; X = H, I, or *i*-C<sub>3</sub>H<sub>7</sub>; n = 0, 1, 2

The 3'-isopropyl compound XIII was prepared using the sequence of reactions shown in Chart I.

Ethyl 3,5-diiodo-4-(3-isopropyl-4-methoxyphenoxy)-phenylacetate (XVI) was first prepared using a procedure (XIV  $\rightarrow$  XV  $\rightarrow$  XVI) similar to that reported by Wilkinson<sup>12</sup> in the preparation of 3,5-diiodothyroacetic acid. The intermediate XVI was prepared subsequently without isolation more expeditiously from the iodonium salt XVII as shown (XVII  $\rightarrow$  XVI) using the method of Ziegler and Marr.<sup>13</sup> Basic hydrolysis of XVI yielded the methoxy acid XIX which in turn could be converted to the hydroxy acid XVIII on treatment with a mixture of acetic and hydriodic acids. The acid XVIII, however, was usually prepared directly from XVI as shown. Treatment of the acids XVIII and XIX with  $\beta$ -diethylaminoethyl chloride as described yielded the corresponding basic esters XIII and XX. Unfortunately, we were unable to purify XX to the point where satisfactory analytical data could be obtained.

Those 4'-methoxy acids whose syntheses had not been reported were readily prepared using dimethyl sulfate and aqueous sodium hydroxide (Table II).

(1) W. R. Rueggauer, M. E. Alpert, and F. R. Silverman, *Endocrinology*, **66**, 160 (1960).

(2) W. F. J. Cuthbertson, P. V. Elcoate, D. M. Ireland, D. C. B. Mills, and P. Shearley, *J. Endocrinol.*, **21**, 45 (1960).

(3) P. Starr, *Clin. Pharmacol. Therap.*, **1**, 716 (1960).

(4) W. R. Rueggauer and F. R. Silverman, *Endocrinology*, **68**, 564 (1961).

(5) M. M. Best and C. H. Duncan, *Circulation*, **24**, 58 (1961).

(6) C. M. Greenberg, C. A. Bocher, J. F. Kerwin, S. M. Greenberg, and T. H. Lin, *Am. J. Physiol.*, **201**, 732 (1961).

(7) R. G. Herman, C. C. Lee, and R. Parker, *Arch. Intern. Pharmacodyn.*, **133**, 284 (1961).

(8) H. R. Hoff, R. J. Sperber, S. Fisch, and A. C. DeGraff, *Angiology*, **13**, 34 (1962).

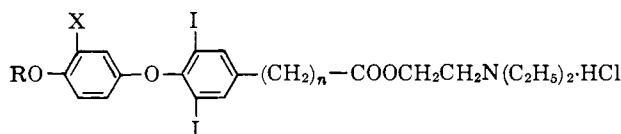
(9) C. H. Duncan and M. M. Best, *Am. J. Clin. Nutr.*, **10**, 297 (1962).

(10) B. Blank, F. R. Pfeiffer, C. M. Greenberg, and J. F. Kerwin, *J. Med. Chem.*, **6**, 554 (1963).

(11) H. Horenstein and H. Püldicke, *Chem. Ber.*, **71**, 1644 (1938).

(12) J. H. Wilkinson, *Biochem. J.*, **68**, 601 (1956).

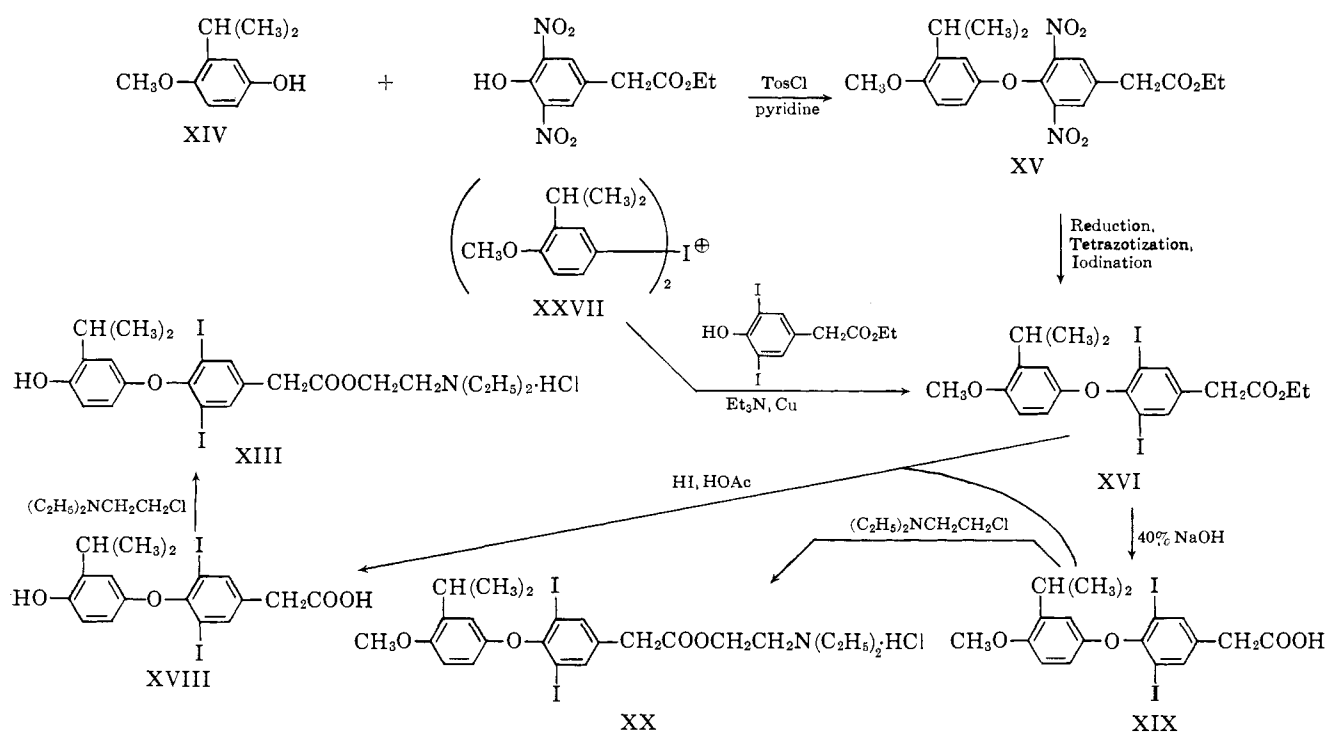
(13) H. Ziegler and C. Marr, *J. Org. Chem.*, **27**, 3335 (1962).

TABLE I  
 DIETHYLAMINOETHYL ESTERS


Com- pound	R	X	n	M.p., °C.	Recryst. solvent	Formula	Source of start- ing matl.	Analyses, %					
								Calcd.			Found		
								C	H	Cl	C	H	Cl
I	H	H	0	220-222	CH <sub>3</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>19</sub> H <sub>22</sub> ClI <sub>2</sub> NO <sub>4</sub>	a, b, c	36.95	3.59	5.74	37.35	3.45	5.79
II	CH <sub>3</sub>	H	0	185-187	CH <sub>3</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>20</sub> H <sub>24</sub> ClI <sub>2</sub> NO <sub>4</sub>	d, e	38.03	3.83	5.61	38.07	3.82	5.53
III	H	I	0	203-205	CH <sub>3</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>19</sub> H <sub>21</sub> ClI <sub>3</sub> NO <sub>4</sub>	e, f	30.69	2.85	4.77	30.97	2.95	4.79
IV	CH <sub>3</sub>	I	0	171-173	CH <sub>3</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>20</sub> H <sub>23</sub> ClI <sub>3</sub> NO <sub>4</sub>	g	31.71	3.06	4.68	32.02	3.04	4.53
V	H	H	1	114-117	<i>i</i> -C <sub>3</sub> H <sub>7</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>20</sub> H <sub>24</sub> ClI <sub>2</sub> NO <sub>4</sub>	c, f, h, i	38.03	3.83	5.61	38.30	4.18	5.37
VI	CH <sub>3</sub>	H	1	149-151	CH <sub>3</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>21</sub> H <sub>26</sub> ClI <sub>2</sub> NO <sub>4</sub>	c, h	39.06	4.06	5.49	39.28	4.23	5.23
VII	H	I	1	192-194	CH <sub>3</sub> OH-petroleum ether	C <sub>20</sub> H <sub>23</sub> ClI <sub>3</sub> NO <sub>4</sub>	f, h	31.71	3.06	4.68	31.70	3.18	4.61
VIII	CH <sub>3</sub>	I	1	189-191	<i>i</i> -C <sub>3</sub> H <sub>7</sub> OH	C <sub>21</sub> H <sub>25</sub> ClI <sub>3</sub> NO <sub>4</sub>	j	32.69	3.27		33.01	3.56	
IX	H	H	2	193-195	CH <sub>3</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>21</sub> H <sub>25</sub> ClI <sub>2</sub> NO <sub>4</sub>	b, c, e k, l	39.06	4.06	N, 1.82	39.14	4.22	N, 2.09
													5.49
X	CH <sub>3</sub>	H	2	145-147	CH <sub>3</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>22</sub> H <sub>28</sub> ClI <sub>2</sub> NO <sub>4</sub>	g	40.05	4.28	5.37	39.78	4.45	5.21
XI	H	I	2	208-210 dec.	CH <sub>3</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>21</sub> H <sub>25</sub> ClI <sub>3</sub> NO <sub>4</sub> · 1.5H <sub>2</sub> O	b	31.58	3.47		31.49	3.42	
XII	CH <sub>3</sub>	I	2	194-195	CH <sub>3</sub> OH-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>22</sub> H <sub>27</sub> ClI <sub>3</sub> NO <sub>4</sub>	g	33.63	3.46	4.51	33.75	3.53	4.85
XIII	H	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	1	133-135	(CH <sub>3</sub> ) <sub>2</sub> CO-H <sub>2</sub> O	C <sub>23</sub> H <sub>29</sub> I <sub>2</sub> NO <sub>4</sub> · 0.5H <sub>2</sub> SO <sub>4</sub>	m	40.25	4.41		40.21	4.29	

<sup>a</sup> C. R. Harington and G. Barger, *Biochem. J.*, **21**, 169 (1927). <sup>b</sup> J. C. Clayton, G. F. H. Green, and B. A. Hems, *J. Chem. Soc.*, 2467 (1951). <sup>c</sup> R. I. Meltzer, D. M. Lustgarten, and A. Fishman, *J. Org. Chem.*, **22**, 1577 (1957). <sup>d</sup> E. T. Borrow, J. C. Clayton, and B. A. Hems, *J. Chem. Soc.*, S 185 (1949). <sup>e</sup> K. Tomita and H. A. Lardy, *J. Biol. Chem.*, **219**, 595 (1956). <sup>f</sup> C. R. Harington and R. Pitt-Rivers, *Biochem. J.*, **50**, 438 (1952). <sup>g</sup> Table II and Experimental. <sup>h</sup> See ref. 12. <sup>i</sup> See ref. 13. <sup>j</sup> K. Tomita, H. A. Lardy, D. Johnson, and A. Kent, *J. Biol. Chem.*, **236**, 2981 (1961). <sup>k</sup> S. Wawzonek, S. C. Wang, and P. Lyons, *J. Org. Chem.*, **15**, 593 (1950). <sup>l</sup> N. Kharasch, S. H. Kalfayan, and J. D. Arterberry, *ibid.*, **21**, 925 (1956). <sup>m</sup> See Experimental.

CHART I



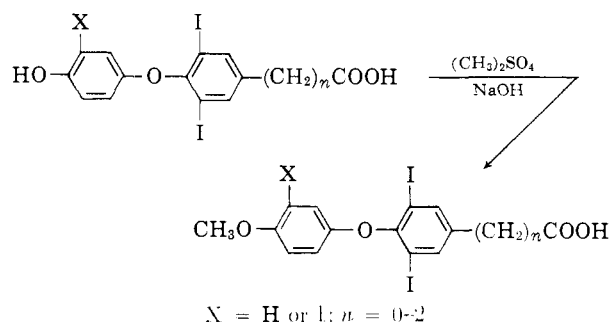


TABLE II  
4'-METHOXY ACIDS

X	n	M.p., °C.	Recrystal. solvent	Formula	Analyses, %			
					Calcd.		Found	
I	0	295-297	C <sub>2</sub> H <sub>5</sub> OH-H <sub>2</sub> O	C <sub>18</sub> H <sub>15</sub> I <sub>2</sub> O <sub>4</sub>	27.04	1.46	27.38	1.40
II	2	170-172	C <sub>2</sub> H <sub>5</sub> OH	C <sub>20</sub> H <sub>17</sub> I <sub>2</sub> O <sub>4</sub>	36.67	2.60	36.07	2.83
I	2	224-226	CH <sub>3</sub> OH	C <sub>18</sub> H <sub>15</sub> I <sub>2</sub> O <sub>4</sub>	29.56	2.02	29.71	2.17

### Experimental<sup>14</sup>

**Chemistry. Preparation of Esters (Table I).**—The required acid in dry 2-propanol was refluxed for 4 hr. in the presence of a slight molar excess of  $\beta$ -diethylaminoethyl chloride.<sup>15,16</sup> The reaction mixture was cooled and the amino ester hydrochloride was filtered and washed with ether. In some cases it was necessary to dilute the reaction mixture with ether or petroleum ether or to partially remove the solvent to ensure complete precipitation of the product. Two recrystallizations usually provided material of analytical purity.

**Ethyl [4-(3-Isopropyl-4-methoxyphenoxy)-3,5-dinitrophenyl]acetate (XV).**—A solution of equimolar amounts of ethyl 4-hydroxy-3,5-dinitrophenylacetate<sup>12</sup> and *p*-toluenesulfonyl chloride in pyridine was heated and stirred on a steam bath for 15 min. The steam bath was removed and a slight excess of 3-isopropyl-4-methoxyphenol (XIV)<sup>10</sup> was added. The solution was stirred under reflux for 2 hr. and the pyridine was then removed *in vacuo*. The residue was dissolved in benzene and the benzene solution was washed in turn with dilute hydrochloric acid, water, 10% sodium hydroxide, and again with water. After drying over sodium sulfate, the benzene was removed and the oily residue was crystallized and recrystallized from 95% ethanol to give 55% of product, m.p. 79-81°.

*Anal.* Calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>8</sub>: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.56; H, 5.37; N, 6.89.

**Ethyl 3,5-Diiodo-4-(3-isopropyl-4-methoxyphenoxy)phenylacetate (XVI).**—The dinitro ester XV was reduced catalytically in a Parr apparatus in the presence of 10% palladium-on-charcoal. The resulting diamino compound without isolation was tetrazotized with nitrosyl sulfuric acid, and the tetrazonium salt was iodinated as described by Wilkinson.<sup>12</sup> The crude diiodo ester XVI was dissolved in benzene, and the benzene solution was washed successively with 10% sodium bisulfite, water, 5% sodium bicarbonate, and again with water. Evaporation of the dried benzene solution yielded a brown oil which was redissolved in a small volume of benzene and was passed through a column of Woelm acid-alumina (activity-1)<sup>17</sup> using 10% methanol in

benzene. Evaporation of the fractions from the column left a reddish oil which crystallized from aqueous ethanol to give 42% of crude product, m.p. 65-74°. Further recrystallizations from methanol or aqueous ethanol gave material melting at 55-76°.

*Anal.* Calcd. for C<sub>26</sub>H<sub>25</sub>I<sub>2</sub>O<sub>4</sub>: C, 41.40; H, 3.82; I, 43.75. Found: C, 41.47; H, 3.82; I, 43.42.

The same material was obtained from the reaction of di-3-isopropyl-4-methoxyphenyliodonium iodide (XVII)<sup>18</sup> with ethyl 4-hydroxy-3,5-diiodophenylacetate<sup>13</sup> in the presence of triethylamine and copper powder.

**3,5-Diiodo-4-(3-isopropyl-4-methoxyphenoxy)phenylacetic Acid (XIX).**—A suspension of 3.0 g. (5  $\mu$ moles) of XVI in 50 ml. of ethanol was diluted with 10 ml. of 40% sodium hydroxide and stirred at room temperature for 2 hr. The solution was cooled and acidified with dilute hydrochloric acid. The precipitated acid was filtered, washed with water, and recrystallized from aqueous ethanol to give 2.0 g. (74%) of product, m.p. 136-138°. (analytical sample, m.p. 142-144°).

*Anal.* Calcd. for C<sub>18</sub>H<sub>15</sub>I<sub>2</sub>O<sub>4</sub>: C, 39.15; H, 3.29; I, 45.97. Found: C, 39.47; H, 3.30; I, 45.56.

**[4-(4-Hydroxy-3-isopropylphenoxy)-3,5-diiodophenyl]acetic Acid (XVIII).**—A mixture of 4.0 g. (6.9  $\mu$ moles) of XVI in 100 ml. of a 1:1 mixture of acetic and hydriodic acids was refluxed for 3 hr. The solution was concentrated to one-half its original volume when solid began to separate. The mixture was diluted with water and cooled. The filtered solid weighed 3.5 g., m.p. 157-159°. It was recrystallized from aqueous ethanol to give 3.2 g. (95%) of product, m.p. 162-164°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>15</sub>I<sub>2</sub>O<sub>4</sub>: C, 37.94; H, 3.00; I, 47.17. Found: C, 38.10; H, 3.03; I, 46.88.

**Preparation of 4'-Methoxy Acids (Table II).**—To a stirred solution of 0.01 mole of the iodinated thyroalkanoic acid in 70 ml. of water and 15 ml. of 10% sodium hydroxide was slowly added at room temperature 0.005 mole of dimethyl sulfate. After stirring for 15 min. an additional 0.005 mole of dimethyl sulfate was added to the cloudy solution followed by the addition of 120 ml. of 10% sodium hydroxide. The solution was stirred for 2 hr. at room temperature during which time the sodium salt precipitated. This mixture was diluted with 100 ml. of 10% sodium hydroxide and 135 ml. of ethanol and stirred under reflux for 2 hr. to hydrolyze any ester. The alcohol was removed and the aqueous residue was cooled to precipitate the sodium salt. The salt was filtered and dissolved in hot water. The aqueous solution was filtered if necessary, cooled, made acid with dilute hydrochloric acid, and filtered. The white solid after two recrystallizations was usually analytically pure.

**Biochemical Screening.**—The compounds were screened for their ability to lower plasma cholesterol levels in rats fed a diet containing 2% cholesterol and 1% cholic acid.<sup>6</sup>

L-Triiodothyronine (L-T<sub>3</sub>) or the test compounds were injected subcutaneously, once daily for 7 days to groups of eight adult male Sprague-Dawley rats having a fasting body weight of 270-290 g. and fed a diet consisting of 2% cholesterol, 1% cholic acid, 4% Alphacel, 4% vitamins and minerals, 20% protein, 20% hydrogenated fat, and 49% carbohydrate. Appropriate controls were also run. The animals were fasted for 18 hr. on the 7th day and sacrificed by decapitation on the 8th day. Blood collections and cholesterol determinations were made in a manner similar to that reported previously.<sup>6,9</sup> The results are shown in Table III and are expressed in terms of L-T<sub>3</sub> having an arbitrary value of 1.

$$\text{activity} = \frac{\text{dose of L-T}_3 \text{ which decreased plasma total cholesterol at least 38 mg./100 ml.}^9}{\text{dose of test compound which lowers plasma total cholesterol to a comparable extent}}$$

### Discussion

Several of the compounds tested lowered plasma cholesterol to some degree. However, there seems to be no doubt that VII and XIII, the diethylaminoethyl esters of 3,3',5-triiodo- and 3,5-diiodo-3'-isopropyl-

(18) C. M. Greenberg, L. F. Mansor, C. A. Bocher, G. L. Saunders, and J. F. Kerwin, *Endocrinology*, **70**, 365 (1962).

(19) It has been shown statistically using pooled samples from thyrotoxic treated and control animals that a plasma total cholesterol difference of 38 mg./100 ml. is required for significance ( $P = 0.01$ ). See ref. 6. A dose of 1.5-3.0  $\mu$ g./kg./day of L-T<sub>3</sub> consistently causes such a depression.

(14) All melting points were taken in a Thomas-Hoover melting point apparatus and are corrected.

(15) This material was conveniently prepared by grinding together with a mortar and pestle one part of commercial  $\beta$ -diethylaminoethyl chloride hydrochloride and two parts of potassium hydroxide pellets in a suitable volume of benzene with cooling if necessary. The benzene solution was decanted or filtered, the solvent was removed, and the residue was distilled at reduced pressure.

(16) R. R. Burtner, *J. Am. Chem. Soc.*, **71**, 2587 (1949).

(17) Aluphaco Chemicals, P. O. Box 755, New Orleans, Louisiana.

thyoacetic acids, were the most potent compounds tested. In the test system employed, VII and XIII were as potent as L-T<sub>3</sub>, one of the most active hypocholesteremic thyromimetic agents reported in the literature.

It can be seen that replacement of the 3'-iodine atom in VII with an isopropyl group has had no effect on hypocholesteremic activity (compare VII with XIII). This finding is consistent with previous observations noted with compounds containing an alanine side chain.<sup>10</sup> Although the number of compounds screened was quite small it appears that a structure-function relationship does exist. Maximum activity resides in those compounds with a two-carbon side chain and a 3'-iodine atom or isopropyl group (VII, VIII, and XIII). Increasing or decreasing the length of the side chain or replacing the 3'-iodine or isopropyl group with hydrogen decreases cholesterol-lowering activity. Formation of the methyl ether in most cases also somewhat lessens hypocholesteremic activity (compare VII with VIII).

A more comprehensive study of the thyromimetic activities of VII and XIII has been reported recently.<sup>20</sup>

TABLE III  
PLASMA CHOLESTEROL VALUES

Compound no.	Activity <sup>a</sup>
I	0.030
II	< .001
III	.030
IV	.040
V	.025
VI	.006
VII	1.000
VIII	0.500
IX	< .001
X	< .001
XI	.060
XII	.030
XIII	1.000

<sup>a</sup> Activity is expressed in terms of L-T<sub>3</sub> having an arbitrary value of 1.

**Acknowledgment.**—We wish to express our gratitude to Mr. Roger O'Connor for technical assistance throughout this study. We also wish to thank Mrs. Doris Ralston and staff for elemental analyses.

(20) C. M. Greenberg, B. Blank, F. R. Pfeiffer, and J. F. Pauls. *Am. J. Physiol.*, in press.

## Synthesis, Properties, and Enzymatic Reactions of Some Aminoacyladenines<sup>1</sup>

JOHN J. BRINK<sup>2</sup> AND ARNOLD H. SCHEIN

*Department of Biochemistry, University of Vermont, College of Medicine, Burlington, Vermont*

*Received May 3, 1963*

A series of aminoacyladenines was prepared by a procedure involving the condensation of the carbobenzoxy derivatives of glycine, alanine, valine, leucine, isoleucine, and phenylalanine with adenine by the carbodiimide method with dimethyl sulfoxide as the solvent. Chemical, spectral, and chromatographic characteristics of the above compounds are described. Neither rat organ homogenates nor a variety of proteolytic enzymes hydrolyzed the aminoacyladenines, with the exception of leucine aminopeptidase, which showed activity against L-leucyladenine.

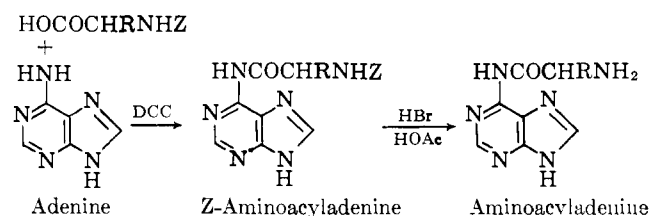
Interest in aminoacylamidopurines and specifically aminoacyladenines stems from the observation that ribonucleic acids (RNA) isolated by a variety of methods contain amino acids or peptides.<sup>3-5</sup> Aside from the binding of amino acids by ester linkage to the terminal ribose moiety of soluble RNA,<sup>6</sup> other binding sites have not been definitely established. It is conceivable that high molecular weight RNA may bind amino acids as acid anhydrides similar to the amino acid nucleotidates found in yeast<sup>7</sup> or as amides by combination of the carboxyl group of the amino acids with the amino nitrogen of adenine, guanine, and the cytosines.

This paper describes the synthesis and properties of a series of aminoacyladenines as a preliminary step in establishing whether or not such compounds occur in

nucleic acids or nucleoproteins.

### Results and Discussion

The aminoacyladenines were prepared by condensing a carbobenzoxyamino acid (Z-amino acid) and adenine in dimethyl sulfoxide solution with N,N'-dicyclohexylcarbodiimide (DCC) and decarboxylating the product with anhydrous HBr in glacial acetic acid.



The values for C, H, and N (Table I) of both carbobenzoxy- and aminoacyladenines support a structure having an amino acid:adenine ratio of 1.

The physical properties and behavior on paper chromatograms of both carbobenzoxy- and aminoacylade-

(1) This investigation was supported in part by the Office of Naval Research and by Vermont Cancer Society Grant No. 6, 1960-1961.

(2) Stanford Research Institute, Menlo Park, California. This work was taken in part from a doctoral dissertation presented to the Graduate College of the University of Vermont, 1962.

(3) J. L. Potter and A. L. Dounce, *J. Am. Chem. Soc.*, **78**, 3078 (1956).

(4) V. Habermann, *Biochim. Biophys. Acta*, **32**, 297 (1959).

(5) U. Z. Littauer and H. Eisenberg, *ibid.*, **32**, 320 (1959).

(6) M. Hoagland, *ibid.*, **16**, 288 (1955).

(7) A. H. Cook and G. Harris, *Rev. Pure Appl. Chem.*, **10**, 61 (1960).