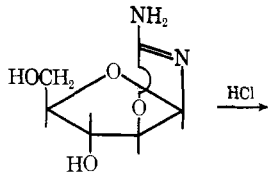
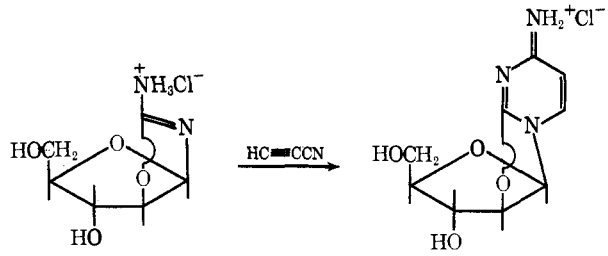


I



II·HCl

II·HCl crystallized from the reaction mixture in pure form. The conversion of the aminooxazoline I to its hydrochloride greatly reduces its nucleophilicity, of course, and heating for several hr is required to obtain condensation with cyanoacetylene and subsequent cyclization to the HCl salt of II. On the other hand, the free base of the aminooxazoline I reacts exothermically with cyanoacetylene, and base-catalyzed conversion to *ara*-C *via* the intermediate anhydro compd II is complete within a few min.[10]

Since completion of this work, Sanchez, *et al.*, have reported the preparation of $O^2,O^{2'}$-anhydroarabinofuranosylcytosine by a process that involves condensation of cyanoacetylene with the aminooxazoline I followed by isolation of the anhydro derivative as its acetate salt.[13]

The L analog of *ara*-C was inactive (at doses of up to 300 mg/kg per day ip daily for 5 days) when tested *in vivo* in the mouse as an antileukemic agent against L1210. The method employed in studying the effect of agents on survival of L1210 leukemic mice was similar to that described by the Cancer Chemotherapy National Service Center.[14] The L analog proved to be inactive as an immunosuppressant at 200 mg/kg ip and po when tested in the mouse hemagglutinin test as described by Gray, *et al.*[15] It neither potentiated nor inhibited the activity of *ara*-C in this test. It was inactive as an antiviral agent in the *in vitro* cell culture test described by Renis, *et al.*[16]

These results parallel those with other L-nucleosides. Yamaoka, *et al.*, have prepared the 1-α-L-arabinofuranosyl derivatives of thymine, cytosine, and uracil.[17] Preliminary screening studies of the L-nucleosides showed no significant activity against L1210 mouse leukemia or Burkett's tumor cells in tissue culture. The cytosine nucleoside was not deaminated by human liver or mouse kidney homogenates, nor did it inhibit the deamination of 1-β-arabinofuranosylcytosine in those systems.[17] These workers also prepared the α-L-xylo and α-L-lyxo derivatives of thymine, uracil, and cytosine, and obtained identical results in biological studies with those obtained with the 1-α-arabinofuranosyl derivatives.[17] Smrž and Farkaš have reported that 1-α-L-lyxofuranosylthymine is not cleaved by nucleoside phosphorylase from *Escherichia coli*.[18] The $O^2,O^{2'}$-anhydro derivative of *ara*-C was active against herpes virus *in vitro*, but was inactive against several RNA viruses. This compd showed no activity in the hemagglutinin test in the mouse when administered ip at 200 mg/kg, but showed some inhibition when given orally on days 1–5 at 200 mg/kg.

When it was administered as a single 200 mg/kg ip dose to L1210 leukemic mice one day after tumor inoculation, a 46% increase in life span (ILS) was obtained. Oral administration (single 500 mg/kg dose) yielded a 39% ILS. The corresponding results with *ara*-C under the same conditions (doses, routes, schedules) were 20 and 28% ILS, respectively.

Experimental Section[19]

2-Amino-β-L-arabinofurano[1′,2′:4,5]-2-oxazoline.—L-(+)-Arabinose (45 g, 0.3 mole) and 25.2 g (0.6 mole) of cyanamide were stirred in a mixt of 15 ml of 6 *M* NH_4OH and 75 ml of MeOH for 5 hr at room temp. The mixt was stored for 72 hr in the cold with stirring, then cooled in an ice–salt bath for several hr. The solid was collected, washed with cold MeOH and then Et_2O, and air-dried. The yield was 25.3 g (47%); mp 179–180° dec; $[\alpha]_D^{25}$ −21° (*c* 1, H_2O). *Anal.* ($C_6H_{10}N_2O_4$) C, H, N. The nmr and ir spectra were superimposable on those for the D compd.[10]

1-β-L-Arabinofuranosylcytosine·HCl (L-*ara*-C·HCl) was prepd as described for D-*ara*-C·HCl,[10] substituting 2-amino-β-L-arabinofurano[1′,2′:4,5]-2-oxazoline for the D isomer. The product was recrystd from DMF–EtOAc: yield, 52%; mp 198–200° dec. A sample was recrystd from MeOH for analysis; mp 200° dec; $[\alpha]_D^{25}$ − 130° (*c* 1, H_2O) (+129° for the D form[1a]). *Anal.* ($C_9H_{13}N_3O_5$·HCl) C, H, N, Cl.

$O^2,O^{2'}$-Anhydro-1-β-D-arabinofuranosylcytosine·HCl.—2-Amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (52.2 g, 0.3 mole) was suspended in 300 ml of MeOH and 27.0 ml of concd HCl was added. The mixt was stirred to effect soln, and the solvent was evapd *in vacuo*. The hydrochloride of the oxazoline was obtained as a glassy residue, which was further dried *in vacuo*. This material was dissolved in 300 ml of DMF, and about 17 g (10% excess) of cyanoacetylene[10] was added. The soln was heated at 95° for 2 hr to effect cyclization. During this time the product sepd as a white cryst solid. The mixt was cooled, the product was collected, washed with DMF and then Et_2O, and dried: yield, 41.5 g (53%); mp 260° dec (lit., 248–250° dec;[1b] 260° dec[12]); $[\alpha]_D^{25}$ −79° (*c* 1, DMSO). *Anal.* ($C_9H_{11}N_3O_4$·HCl) C, H, N, Cl.

Acknowledgments.—We wish to thank Dr. H. E. Renis for the antiviral tests.

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(19) Where analyses are indicated only by symbols of the elements, anal. values obtained for those elements were within ±0.4 of theor values.

4(5)-(2-Amino-1-hydroxyalkyl)imidazoles[1a]

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While much work has been done on the changes in pharmacodynamic action in the catecholamine series

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by introduction of alcoholic OH groups in the alkylamine chain, very little attention has been paid to the parallel series of histamine derivatives. Pyman, as early as 1916, prepared β-hydroxyhistamine;[2] this was tested by Dale and found to be "less active in its sympathomimetic action than histamine." No further work has been done on this system. We have now synthesized a series of amino alcohol analogs of histamine for further testing.

The synthesis of these amino alcohols was carried out by one of two different pathways, both involving the preparation of *N*-triphenylmethyl-4-imidazolecarboxaldehyde (**1**). Trityl protection served to prevent the secondary amino group of the imidazole ring from interfering in any of the subsequent steps. The trityl group was chosen as the blocking agent in view of the excellent results in protection and subsequent easy deprotection found in previous experiences in the imidazole system.[3]

The synthesis of imidazolyl amino alcohols with a primary amino group was accomplished by way of the corresponding nitro alcohols. Thus, condensation of **1** with $MeNO_2$ or $EtNO_2$, using a modification of the method of Nagai and Kanao,[4] led to the respective nitro alcohols (**2**, **3**). Reduction of these with LAH in THF, followed by acid removal of the trityl group, afforded β-hydroxyhistamine (**4**) and α-methyl-β-hydroxyhistamine (**5**), resp, isolated as the dihydrochlorides. The last product was obtained only in 20–25% yield, due to a reversion of the reaction during the reduction with LAH, from which **1** and $EtNO_2$ were formed back and reduced *in situ*. The main product of the reaction was, thus, 4-(*N*-trityl)imidazolylmethanol (**6**), which was identified by comparison with an authentic sample prepared by direct reduction of **1**. The same reversal of reaction was observed in the case of the nitro alcohol **2**, although **6** was obtained here in a very small amount only.

In the preparation of secondary and tertiary amino alcohols, **1** was treated with dimethylsulfonium methylide[5,6] and the resulting 1-triphenylmethyl-4-imidazolyloxirane (**7**) was isolated in almost quantitative yield. Treatment of this epoxide with amines furnished trityl-protected secondary and tertiary amino alcohols, which were transformed into N-substituted β-hydroxyhistamines by gentle acid treatment. Following this method, 1-(4-imidazolyl)-2-(*N*-methylamino)- (**8**), -2-(*N*-isopropylamino)- (**9**), and -2-(*N*,*N*-dimethylamino)ethanol (**10**) were obtained.

Pharmacology.†—In the isolated perfused rabbit heart, the primary ($CHOHCH_2NH_2$, **4**) and secondary ($CHOHCH_2NHCH_3$, **8**) amines produced tachycardia and a very modest dilation of the coronary vessels (*i.e.*, modest antianginal action) but had no β-blocking activity (no block of isuprel tachycardia). The tertiary amine ($CHOHCH_2NMe_2$, **10**) did not cause an appreciable increase in heart rate and did suppress substantially the tachycardia produced by a standard dose (3×10^{-7} *M*) of isuprel suggesting some block of β receptors in the heart. The *N*-isopropyl derivative ($CHOHCH_2NH$-*i*-Pr, **9**) at 10^{-4} *M*, slightly inhibited (heart rate 138) isuprel tachycardia (heart rate 150), but in itself had no effect on heart rate or coronary flow.

Experimental Section

Melting points were detd in a Uni-Melt capillary melting point apparatus and are cor. Ir spectra were recorded on a Perkin-Elmer spectrophotometer Model 337 in KBr, nmr spectra on a Hitachi Perkin-Elmer R-20, in $DCCl_3$ (TMS) or in D_2O (DSS as internal standard) in the case of the salts of the amines. Ir and nmr spectra were taken for all compds and confirmed the reported structures. Analyses by Galbraith Laboratories, Knoxville, Tenn.

4-(*N*-Triphenylmethyl)imidazolecarboxaldehyde (**1**).—To a stirred soln of 24 g (0.25 mole) of 4-imidazolecarboxaldehyde and 26 g (0.26 mole) of Et_3N in 300 ml of $CHCl_3$, 72 g (0.26 mole) of Ph_3CCl was added. An exothermic reaction took place. The resulting soln was stirred at room temp overnight, washed (H_2O), and dried (Na_2SO_4), and the solvent was removed *in vacuo* to give a colorless solid (67 g). Recrystn (EtOH) gave an anal. sample.

1-[4-(*N*-Triphenylmethyl)imidazolyl]-2-nitroethanol (**2**).—To 11.2 g (0.033 mole) of **1**, dissolved in 150 ml of dioxane and 30 ml of H_2O, 6 g (0.099 mole) of $MeNO_2$ and 0.75 g of $NaHCO_3$ were added. The mixt was stirred at room temp. After a few hr, a white solid began to deposit. After stirring for 40–45 hr, the solid was collected (8.5 g). Recrystn from MeOH afforded an anal. sample. On addn of H_2O to the mother liquors, a second crop of **2** was obtd, total yield 10.5 g.

1-[4-(*N*-Triphenylmethyl)imidazolyl]-2-nitropropanol (**3**).—By the same method, using 12 g (0.036 mole) of **1** and 8 g (0.107 mole) of $EtNO_2$, 10.1 g of **3** was obtd. Recrystn from a large vol of EtOH gave material, mp 143–145°. Nmr showed the product contd EtOH of crystn. After drying, the mp rose to 195–197°.

β-Hydroxyhistamine[2] (**4**).—To a slurry of 0.3 g of LAH in 25 ml of THF, a soln of 1.5 g (0.003 mole) of **2** in 20 ml of THF was added dropwise. After 10 min of stirring at room temp the mixt was refluxed for 8 hr and cooled, and 10 ml of H_2O was added cautiously. After 30 min, the mixt was filtered, and the inorg salts were washed (THF). After drying (Na_2SO_4) the filtrate was evapd, affording a syrup which was dissolved in 50 ml of Et_2O and extd with 1 *N* HCl (20 + 5 ml). The acid soln was counterextd with $CHCl_3$. Heating for 15 min on a steam bath caused pptn of Ph_3COH, which was filtered off. The soln of **4**·2HCl was treated with active charcoal and filtered, and H_2O was removed *in vacuo*. The dihydrochloride crystd from abs EtOH as tan needles. Recrystn (MeOH–Et_2O) gave an anal. sample, mp 214–216° dec (reported[2] 216° dec). In two other runs, the yield was 60–65%.

The **dipicrate,** prepd in H_2O, crystd upon cooling, mp 224–226° dec (reported[1] mp 225° dec).

A small amount of **4**·2HCl was synthesized according to Pyman[2] but the cyanohydrin of 4-imidazolecarboxaldehyde was reduced with LAH, instead of NaHg. The mp and ir spectra of both compds were identical.

α-Methyl-β-hydroxyhistamine (**5**).—To a stirred slurry of 0.5 g of LAH in 25 ml of THF, a soln of 2.4 g (0.006 mole) of **3** in THF was added dropwise. The soln turned red. After stirring for 0.5 hr at room temp, the soln was refluxed for 5 hr and cooled, and 10 ml of H_2O was added. The insol salts were filtered off and washed (THF). The soln was dried (Na_2SO_4), and the solvent was removed *in vacuo*. The oil was characterized as the dipicrate and dihydrochloride; yields 20–25%.

The Et_2O and $CHCl_3$ exts were collected, washed (H_2O), and dried (Na_2SO_4), and the solvent was removed *in vacuo*. After recrystn from dioxane, the residual colorless solid had mp 234–236°, identical with that of 4-(*N*-triphenylmethyl)imidazolylmethanol (**6**) prepd by reduction of **1** with LAH (*vide infra*). Hydrogenation of **3** with several catalysts under a variety of condns did not increase the yield of amino alcohol **5**.

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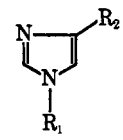
† We are grateful to Dr. James W. Wilson of Smith Kline and French Laboratories, Philadelphia, Pa., for permission to summarize test results furnished by his associates.

TABLE I

IMIDAZOLYL DERIVATIVES



No.	R_1	R_2	Mp, °C	Yield, %	Solvent of recrystn	Formula[c]
1	CPh_3	CHO	197–199	80	EtOH	$C_{23}H_{18}N_2O$
2	CPh_3	$CHOHCH_2NO_2$	182–183	88	MeOH	$C_{24}H_{21}N_3O_3$
3	CPh_3	$CHOHCH(CH_3)NO_2$	195–197	68	EtOH	$C_{25}H_{23}N_3O_3$
6	CPh_3	CH_2OH	234–236	80	Dioxane	$C_{23}H_{20}N_2O$
7	CPh_3	c-$CHOCH_2$	194–196	100	EtOH	$C_{24}H_{20}N_2O$
4 (salt)	H	$CHOHCH_2NH_2 \cdot 2HCl$[a]	214–216	65	MeOH–Et_2O	$C_5H_{11}Cl_2N_3O$
	H	$CHOHCH_2NH_2 \cdot$ dipicrate[a]	224–226		H_2O	$C_{17}H_{17}N_9O_{16}$
8 (salt)	H	$CHOHCH_2NHCH_3 \cdot$ fumarate[d]	185–187 dec	35	MeOH	$C_{10}H_{13}N_3O_5$
	H	$CHOHCH_2NHCH_3 \cdot$ dipicrate	209–211 dec		H_2O	$C_{18}H_{17}N_9O_{15}$
9 (salt)	H	$CHOHCH_2NHCH(CH_3)_2 \cdot$ difumarate	162–164 dec	65	MeOH	$C_{16}H_{23}N_3O_9$
	H	$CHOHCH_2NHCH(CH_3)_2 \cdot$ dipicrate	190–192 dec		H_2O	$C_{20}H_{21}N_9O_{15}$
5 (salt)	H	$CHOHCH(CH_3)NH_2 \cdot 2HCl$	216–218 dec	25	MeOH–Et_2O	$C_6H_{13}Cl_2N_3O$
	H	$CHOHCH(CH_3)NH_2 \cdot$ dipicrate	204–206 dec		H_2O	$C_{18}H_{17}N_9O_{15}$
10 (salt)	H	$CHOHCH_2N(CH_3)_2 \cdot 2HCl$[b]	173–175	55	MeOH–Et_2O	$C_7H_{15}Cl_2N_3O$
	H	$CHOHCH_2N(CH_3)_2 \cdot$ dipicrate	237–239 dec		H_2O	$C_{19}H_{19}N_9O_{15}$

[a] Ref 2. [b] Slightly hygroscopic. [c] All compds analyzed satisfactorily (±0.4%) for C, H, N. [d] Prepd in a sealed tube at 120° in dioxane.

4-(*N*-Triphenylmethyl)imidazolylmethanol (6).—Compd **1** (2 g, 0.006 mole) was added in portions to a stirred slurry of 0.3 g of LAH in 50 ml of THF. The mixt was refluxed for 2 hr and then allowed to cool, 5 ml of H_2O was added, and the mixt was worked up as usual; yield, 1.6 g (see Table I).

4-(*N*-Triphenylmethyl)imidazolyl]oxirane (7).—The procedures of Corey and Chaykowsky[5] and Duncan, *et al.*,[6] were used. To 3.36 g (0.07 mole) of NaH (50% in paraffin oil) was added 30 ml of DMSO under N_2. The mixt was stirred at 65–70° for 45–60 min and, after cooling, 30 ml of THF was added. The soln was chilled to 0° to −10° and a soln of trimethylsulfonium iodide (14.3 g, 0.07 mole) in 50 ml of DMSO was added dropwise. The mixt was stirred for another 5 min, and 12 g (0.035 mole) of the solid aldehyde **1** was added in portions. After 10 min the cooling bath was removed and stirring contd for 1 hr at 29°. The slurry was poured into a mixt of 500 ml of cold H_2O and 250 ml of petr ether (bp 30–60°), and allowed to stand at 4° overnight. The solid oxirane was filtered, washed (H_2O, petr ether), and air-dried. The yield was practically quant. The product was sufficiently pure for use in the following steps.

***N*-Substituted β-Hydroxyhistamines.**—Compd **7** (0.01 mole) was refluxed in each case for 8 hr with a mixt of 5–10 times the necessary molar amt of primary or secondary amine and enough EtOH or dioxane to keep the oxirane in soln.[6] After cooling, the reaction product was extd several times with Et_2O, and the ext was washed (H_2O) and counterextd with 1 *N* HCl (25 + 10 ml). The aq layer was heated on a steam bath for 15 min, the pptd Ph_3COH was filtered off, and H_2O was evapd *in vacuo*. The residual oil was dissolved in a small amt of abs EtOH. One part was converted to the respective picrate in EtOH.

From another portion, the dihydrochlorides were obtd on cooling, sometimes after addn of abs Et_2O. If they were hygroscopic, their soln in EtOH was made slightly alk (pH 8) with KOH in EtOH, KCl was filtered off, and a soln of excess fumaric acid in boiling MeOH was added. Recrystn from MeOH–Et_2O afforded the corresponding difumarates.

Pharmacological Methods.—Male rabbits (1.1 kg) were used; their isolated heart was suspended in Chenoweth's soln. Isuprel was used at 3×10^{-7} *M*, the drugs were used at 1×10^{-3} to 1×10^{-6} *M*. The reported changes refer to 1×10^{-6} *M* drug solns.

Potential Inhibitors of Protein Biosynthesis

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A structural basis for the inhibition of protein synthesis by emetine and cycloheximide was recently proposed, based on an analogy between the ipecac alkaloids and glutarimide antibiotics.[1,2] Based on this hypothesis, the biological activity of tubulosine was correctly predicted.[3] Compounds **1** and **2** described in this communication embody some but not all topochemical features of the proposed model.

Following esterification of **3**, the Me ester **4** was quaternized with *p*-TsOMe to give **5**. Reduction of **5** in the presence of Pt gave **6**. Homoveratrylamine (**8**) was prepared by condensation of **9** with $MeNO_2$ followed by LAH reduction of **10**.[4] Heating **7** or **8** with **6** afforded the amides (**11** or **12**). These underwent $POCl_3$-induced cyclization to **13** and **14** which afforded

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