TABLE I

PURIFICATION OF 5-DEOXYPYRIDOXAL BY ADSORPTION CHROMATOGRAPHY ON SILICA GEL

Fraction[a]	Eluent: Benzene	Eluent: $CHCl_3$	Wt, g
1–3	100	...	...
4–5	99	1	...
6–7	97	3	...
8–9	95	5	...
10–12	90	10	...
13–21	80	20	1.59
22–24	50	50	0.54
25–33	0	100	2.00

[a] Fractions of approximately 300 ml were collected.

ethanol extract, crystalline III·HCl (9.94 g with double melting points at 139–142° and 146–148°) precipitated. From the mother liquor another 2.47 g of crystals (mp 140–142°) was obtained. The total yield was 87%.

5-Deoxypyridoxal (IV).—Chloroform (50 ml) was overlaid with a solution of 10.2 g of III·HCl in 50 ml of water and stirred at 55°. A thick aqueous suspension of MnO_2 prepared[8] from 13.0 g of $KMnO_4$, and 2.44 ml of concentrated H_2SO_4 were added alternately in small portions over 6 hr so that the pH remained at about 4.5. The lower chloroform layer (which extracts the product as formed) was siphoned off each hour and replaced by fresh chloroform. The course of the oxidation was followed by measuring the absorbance of samples of the two layers in 0.1 *N* aqueous NaOH at 307 mμ (λ_{max} for III) and 390 mμ (λ_{max} for IV).

The chloroform extracts were combined and evaporated *in vacuo*. The residue was extracted with petroleum ether (bp 30–60°) and yielded 4.76 g (58%) of IV, mp 104–110°. The material was further purified by dissolving in benzene, applying to a column containing 150 g of silica gel (Merck, 0.05–0.20 mm), and eluting with benzene containing increasing amounts of chloroform. The desired product appeared in fractions 13–33 (Table I). These fractions were combined and evaporated to dryness, and the residue was crystallized from hot methanol and washed with ether: mp 111.5–113°.

Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.62; H, 6.26; N, 9.34.

(8) M. Viscontini, C. Ebnother, and P. Karrer, *Helv. Chim. Acta*, **34**, 1834 (1951).

N-Oxides of 9-(β-D-Xylofuranosyl)adenine and 9-(β-D-Arabinofuranosyl)adenine[1]

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The antitumor effects of 9-(β-D-arabinofuranosyl)adenine and 9-(β-D-xylofuranosyl)adenine are decreased by their conversion to the biologically inactive hypoxanthine derivatives through enzymatic deamination.[2] A similar result has been observed for 3′-deoxyadenosine[3] (cordycepin), but this deamination could be nearly eliminated through the use of cordycepin 1-oxide. The slow enzymatic reduction back to cordycepin in the tumor cell provided a means of continuous administration of cordycepin to the tumor. In an attempt to provide, similarly, a therapeutically better form of the adenine β-arabinoside and β-xyloside, their 1-oxides were prepared by the methods described in this paper.

Experimental Section[4]

9-(β-D-Xylofuranosyl)adenine 1-Oxide.—A solution of 2.20 g (8.24 mmoles) of 9-β-D-xylofuranosyladenine in 125 ml of glacial acetic acid which contained 11 ml of 30% aqueous H_2O_2 was stored at room temperature for 6 days,[5] then was cooled to 0° and the excess peroxide was decomposed by the cautious addition of 5% Pd–C. The mixture was filtered through Celite, and the filtrate was evaporated to dryness *in vacuo* to give a pale orange solid which was a 3:1 mixture of product and starting material as shown by paper chromatography in solvents A and B. Trituration with several portions of warm methanol removed the starting material to leave 1.0 g (43%) of oxide that was homogeneous on paper chromatography in solvents A and B and had mp 249–250° dec. The analytical sample was obtained by recrystallization from methanol: mp 244–246° dec; $[\alpha]^{28.5}D$ −32° (*c* 1, water); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε11,700); $\lambda_{max}^{pH\ 7}$ 261 mμ (ε 9160); $\lambda_{max}^{pH\ 13}$ 307 mμ (ε 5050), 268 mμ (ε 9400).

Anal. Calcd for $C_{10}H_{13}N_5O_5$: C, 42.4; H, 4.62; N, 24.7. Found: C, 42.2; H, 4.81; N, 24.6.

The product had R_{ad} values of 0.24 and 2.0 on paper chromatography in solvents A and B, respectively, as compared with xylofuranosyladenine which had R_{ad} values of 0.66 and 1.3, respectively.

9-(β-D-Arabinofuranosyl)adenine 1-Oxide.—A solution of 0.50 g (1.87 mmoles) of 9-(β-D-arabinofuranosyl)adenine with 3 ml of 30% H_2O_2 in 25 ml of glacial acetic acid was stored for 10 days at room temperature, then worked up as described for the preparation of 9-(β-D-xylofuranosyl)adenine 1-oxide to give a mixture of product and starting material. Trituration with refluxing 95% ethanol dissolved the bulk of the starting material to yield 0.39 g (74%) of product. Recrystallization from water gave the analytical sample: mp 245–252° dec; $[\alpha]^{28}D$ +15° (*c* 0.5, water); $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 12,200); $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 8650); $\lambda_{max}^{pH\ 13}$ 305 mμ (ε 3790), 267 mμ (ε 8750).

Anal. Calcd for $C_{11}H_{13}N_5O_5$: C, 42.4; H, 4.62; N, 2.47. Found: C, 42.4; H, 4.91; N, 24.5.

Paper chromatography in solvents A and B showed spots at R_{ad} 0.52 and 1.3, respectively, compared to starting material which had R_{ad} 0.22 and 1.9, respectively, and adenine 1-oxide which had R_{ad} 0.41 and 1.4, respectively.

(4) Melting points were taken on a Thomas-Hoover apparatus and are corrected. Paper chromatograms were run by the descending method with adenine used for a standard. Solvent systems were water-saturated butanol (solvent A) and 5% aqueous Na_2HPO_4 (solvent B).

(5) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958).

Esters and Amides from Mannich Ketones

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Reduction of Mannich ketones to the alcohols followed by benzoylation has been reported to give esters possessing local anesthetic action.[2] Some new esters of this type have been synthesized from 2-(*t*-amino)methylcyclohexanol and various acyl chlorides. When the 2-(*t*-amino)methylcyclohexanone was reductively aminated by a modification of the method of Smith and Day[3] and the resulting cyclohexylamine derivative was treated with an acyl chloride, amides corresponding to the esters were formed. All the compounds were isolated as their hydrochlorides and are listed in Table I.

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(2) G. A. LePage and I. G. Junga, *Cancer Res.*, **25**, 46 (1965).

(3) S. Frederiksen, *Biochim. Biophys. Acta*, **76**, 366 (1963).

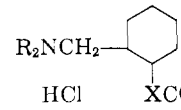
(1) Department of Chemistry and Biology, Welsh College of Advanced Technology, Cathays Park, Cardiff, Wales.

(2) C. Mannich and W. Hof, *Arch. Pharm.*, **265**, 589 (1927); C. Mannich and R. Braun, *Ber.*, **53**, 1874 (1920).

(3) G. W. Smith and A. R. Day, *J. Am. Chem. Soc.*, **77**, 3541 (1955).

TABLE I

2-AMINOMETHYLCYCLOHEXYL DERIVATIVES



No.	X	R′	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % Cl	Found, % C	Found, % H	Found, % Cl
			R_2N = Piperidino							
1	O	4-$MeOC_6H_4$	175–177	$C_{20}H_{30}ClNO_3$	65.3	8.2	9.7	65.0	8.4	9.8
2	O	4-$BuOC_6H_4$	184–185	$C_{23}H_{36}ClNO_3$	67.4	8.9	8.7	67.2	8.9	8.7
3	O	4-$C_6H_5CH_2OC_6H_4$	128–130	$C_{26}H_{34}ClNO_3$	70.3	7.7	8.0	70.2	7.9	7.8
4	O	4-$CF_3C_6H_4$	177–179	$C_{20}H_{27}ClF_3NO_2$	59.2	6.7	8.8	58.9	7.3	8.8
5	O	4-*t*-BuC_6H_4	228–230	$C_{23}H_{36}ClNO_2$	70.1	9.2	9.0	70.0	9.5	8.9
6	O	4-ClC_6H_4	190–192	$C_{19}H_{27}Cl_2NO_2$	61.3	7.3	9.6	61.0	7.5	9.4
7	O	3,4-$(MeO)_2C_6H_3$	210–212	$C_{21}H_{32}ClNO_4$	63.5	8.1	8.9	63.0	8.2	8.8
8	O	3,4,5-$(MeO)_3C_6H_2$	187–189	$C_{22}H_{34}ClNO_5$	61.7	8.0	8.3	61.9	8.2	8.2
9	O	$(C_6H_5)_2C(OH)$	191–193	$C_{26}H_{36}ClNO_4$	67.8	7.8	7.7	68.1	7.8	7.7
10	NH	4-$MeOC_6H_4$	219–221	$C_{20}H_{31}ClN_2O_2$	65.6	8.5	9.7	65.8	8.6	9.7
11	NH	4-$BuOC_6H_4$	175–177	$C_{23}H_{37}ClN_2O_2$	67.5	9.1	8.7	67.9	9.4	8.7
12	NH	4-$C_6H_5CH_2OC_6H_4$	216–217	$C_{26}H_{35}ClN_2O_2$	70.3	7.9	8.0	70.0	8.1	8.1
13	NH	4-*t*-BuC_6H_4	229–231	$C_{23}H_{37}ClN_2O$	70.0	9.2	9.0	70.3	9.5	9.1
14	NH	4-$CH_2{=}CH(CH_2)_3OC_6H_4$	162–163	$C_{24}H_{37}ClN_2O_2$	68.5	8.9	8.4	68.0	8.9	8.5
15	NH	4-$BrCH_2CHBr(CH_2)_3OC_6H_4$	145–147	$C_{24}H_{37}Br_2ClN_2O_2$	49.7	6.4	6.2	50.2	6.6	6.2
16	NH	4-$CH{\equiv}C(CH_2)_3OC_6H_4$	151–153	$C_{24}H_{35}ClN_2O_2$	68.8	8.4	8.5	68.8	8.3	8.5
17	NH	3,4-$(MeO)_2C_6H_3$	225–227	$C_{21}H_{33}ClN_2O_3$	63.6	8.3	8.9	63.8	8.6	8.6
18	NH	3,4,5-$(MeO)_3C_6H_2$	185–188	$C_{22}H_{35}ClN_2O_4$	61.9	8.2	8.3	61.3	8.6	8.5
19	NH	$(C_6H_5)_2C(OH)$	244–245	$C_{26}H_{35}ClN_2O_2$	70.5	8.0	8.0	69.8	7.6	8.4
			R_2N = Morpholino							
20	O	4-ClC_6H_4	177–179	$C_{18}H_{25}Cl_2NO_3$			9.5[a]			9.2[a]
21	NH	4-$MeOC_6H_4$	206–208	$C_{19}H_{23}ClN_2O_2$	62.5	8.3	10.9	62.2	8.7	11.1
22	NH	4-$BuOC_6H_4$	189–191	$C_{22}H_{29}ClN_2O_2$	64.3	8.6	8.6	63.7	8.9	8.9
23	NH	4-$C_6H_5CH_2OC_6H_4$	170–172	$C_{25}H_{33}ClN_2O_3$	67.5	7.5	8.4	67.3	7.5	8.2
24	NH	3,4,5-$(MeO)_3C_6H_2$	204–206	$C_{21}H_{27}ClN_2O_4$	58.8	7.8	8.3	59.0	7.8	8.2

[a] Ionic chlorine.

Experimental Section

Apart from those described below, the carboxylic acids used for preparing the acid chlorides were either commercially available or prepared by published methods.

2-Piperidinomethylcyclohexylamine Dihydrochloride.—To a solution of 2-piperidinomethylcyclohexanone (30 g) in methanol (200 ml) which had previously been saturated with ammonia, was added 5% Pd–C (2 g). This mixture was hydrogenated at 3 atm of pressure until hydrogen uptake ceased. Catalyst and solvent were removed, and the residue was suspended in ice water and acidified with concentrated HCl. Repeated evaporation to dryness under vacuum gave a solid (22.6 g, 55%), mp 251–253°.

***p*-(4-Pentenyloxy)benzoic Acid and Its Chloride.**—Ethyl *p*-hydroxybenzoate (42 g) in ethanol (60 ml) was added to a solution of sodium (5.8 g) in ethanol (160 ml) whereupon the sodium salt precipitated. 1-Bromo-4-pentene[4] (37.7 g) in ethanol (60 ml) was added and the mixture was heated under reflux with stirring for 30 hr. Most of the solvent was distilled, the residue was dissolved in water, and extracted with ether, and the extracts were dried and distilled to give the ethyl *p*-(4-pentenyloxy)benzoate (52.6 g, 85%), bp 122–126° (0.3 mm). Hydrolysis by heating for 30 min with ethanolic KOH gave the acid (40 g, 87%) which separated from aqueous ethanol as colorless crystals, mp 119–121°.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8. Found: C, 69.1; H, 6.9.

The acid chloride, bp 120–130° (0.7 mm), was prepared by reaction with $SOCl_2$.

***p*-(4,5-Dibromopentoxy)benzoic Acid and Its Chloride.**—*p*-(4-Pentenyloxy)benzoic acid (5 g) in chloroform (50 ml) was treated dropwise with bromine (4 g) in $CHCl_3$ (25 ml) with stirring. A white solid separated out; stirring was continued for 30 min after addition of bromine. The solid was collected, washed ($CHCl_3$), and recrystallized from ethanol to give the acid (6.2 g, 70%), mp 166–168°.

Anal. Calcd for $C_{12}H_{14}Br_2O_3$: C, 39.3; H, 3.8. Found: C, 39.1; H, 3.9.

The acyl chloride, bp 202–206° (0.9 mm), was prepared by the usual method using $SOCl_2$.

***p*-(4-Pentynyloxy)benzoic Acid and Its Chloride.**—The above dibromo acid (15 g) was heated under reflux for 24 hr with KOH (7.4 g) in ethanol (40 ml). Water was then added and the ethanol was distilled under reduced pressure. More water was added and the solution was acidified with concentrated HCl. The white precipitate was collected and recrystallized from methanol to give the acetylenic acid (2.1 g, 25%), mp 128–132°. Further purification proved difficult and the acid chloride, bp 206–208° (12 mm), was prepared.

Esters and amides were prepared by mixing the respective cyclohexanol or cyclohexylamine and the acyl chloride in chloroform or benzene and heating the mixture under reflux for about 1 hr. The solvent was distilled and the residue was crystallized from an acetone–ether–methanol mixture.

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(4) P. Gaubert, R. P. Linstead, and H. N. Rydon, *J. Chem. Soc.*, 1971 (1937).