α-Aminomethylpyrazine (IV).—A mixture of 15 g (0.06 mole) of V and 600 ml of 5 *N* NaOH was refluxed 1 hr. The solution was cooled to 10° and extracted with fifteen 50-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined and dried (Na_2SO_4) and the $CHCl_3$ was removed under vacuum. The residual oil was distilled at 87–88° (3 mm) to yield 4.43 g (64.7%) of a colorless liquid, which rapidly turned yellow on standing in the air. *Anal.* ($C_5H_7N_3$) C, H, N.

Reaction of α-Aminomethylpyrazine (IV) with Ethylene Oxide.—To 30.01 g (0.028 mole) of IV cooled to 0° was added 2.73 g (0.062 mole) of liquid ethylene oxide. The reaction flask was sealed and the contents were allowed to stand at room temperature for 24 hr. The brown viscous oil was fractionally distilled to yield four fractions: fraction 1, bp 80–81° (3 mm), was 1.09 g of IV; fraction 2, bp 102–104° (0.1 mm), afforded 1.14 g (42.3%, calculated on the basis of reclaimed IV) of II; fraction 3, a crude intermediate fraction (0.22 g), bp 104–140° (0.1 mm); fraction 4, bp 140–141° (0.1 mm), yielded 0.93 g (26.8%, calculated on the basis of reclaimed IV) of III.

2-(2-Chloroethyl)aminomethylpyrazine Dihydrochloride (VI).—To 0.86 g (0.0037 mole) of II·2HCl was added 5 ml of $SOCl_2$. After standing at 40° for 15 hr, the reaction mixture was allowed to cool, treated with 50 ml of Et_2O, and filtered. The solid was dissolved in MeOH and treated with decolorizing carbon, and the hydrochloride precipitated with Me_2CO; it consisted of 0.74 g (79.5%) of a light green solid which did not melt below 340°. White flakes, melting above 340° dec, were obtained by recrystallization from MeOH–Me_2CO. *Anal.* ($C_7H_{12}Cl_3N_3$) C, H, Cl, N.

The compound proved to be inactive[4] (T/C = 91% at 12 mg/kg) against the 5WA Walker 256 animal tumor screen.

(4) Screening results were supplied by the CCNSC of the National Institutes of Health.

9-(2-Deoxycellobiosyl)adenine[1]

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A number of nucleosides have been reported which are derived from disaccharide sugars. The synthesis of these nucleosides was achieved by coupling of the acetylated bromides or chlorides of lactose,[2,3] cellobiose,[3,4] and maltose[4] with the heavy metal salts of purines or pyrimidines. In one case, that of melibiose,[5] it was found advantageous to use benzoyl blocking groups instead of acetyl groups in order to protect the 1→6 bond of this disaccharide from cleavage during bromination. Especially exciting from a medicinal viewpoint has been the discovery that the antibiotic, amicetin, is a nucleosidic substance containing a disaccharide moiety.[6] The present report describes the first synthesis of a 2-deoxy disaccharide nucleoside, 9-(2-deoxycellobiosyl)adenine [9-(4-*O*-β-D-glucopyranosyl-2-deoxy-D-*arabino*-hexopyranosyl)adenine]. The synthetic route used was based on the one reported by Davoll and Lythgoe[7] for the preparation of 7-(2-deoxy-D-ribopyranosyl)theophylline from diacetyl-D-arabinal.

Experimental Section

Hexa-*O*-acetylcellobial[8] [3.0 g, 5.35 mmoles, mp 132°, $[\alpha]^{27}D$ −21° (*c* 1.4, $CHCl_3$)] was dissolved in 30 ml of Na-dried C_6H_6 and the solution was chilled in an ice bath. Dry HCl gas was passed into the solution for 0.5 hr. C_6H_6 was evaporated at a bath temperature of 30° and fresh, dry C_6H_6 was added and evaporated several times in order to remove traces of HCl. The residual syrup was dissolved in 75 ml of dry xylene and added to an azeotropically dried refluxing mixture of 6-benzamidochloromercuripurine[10] (2.53 g, 5.35 mmoles), 2.5 g of Celite-545, 5 g of Molecular Sieve 4A, and 275 ml of xylene. The mixture was refluxed for 1 hr, the solids were removed by filtration, and the filter cake was washed with 100 ml of warm $CHCl_3$. The solvents were removed by evaporation, the residue was dissolved in 125 ml of $CHCl_3$, and the $CHCl_3$ solution was washed twice with 100-ml portions of 30% aqueous KI and once with 200 ml of H_2O. The solution was dried ($MgSO_4$) and after evaporation of the $CHCl_3$ a dark foam was obtained which weighed 4.8 g.

The foam was dissolved in $CHCl_3$ and applied to the top of a column containing 50 g of silicic acid (Mallinckrodt, 100 mesh, activated at 100° for 24 hr). $CHCl_3$ (375 ml) was passed through the column and discarded. Elution with 300 ml of $CHCl_3$–MeOH (99:1 v/v) followed by 300 ml of a 97:3 v/v mixture of the same solvents yielded 3.66 g of a clear, slightly yellow syrup which was not homogeneous when chromatographed on the plates.[11] The blocking groups were removed by refluxing for 1 hr in 90 ml of 0.1 *N* methanolic $NaOCH_3$ solution. The solution was neutralized (AcOH) and evaporated to dryness. The gummy residue was dissolved in hot MeOH with the aid of a few drops of H_2O. Acetone was added to incipient turbidity, heat from a steam bath was applied to just clarify it, and the flask was placed in a refrigerator for several days. A tan material weighing 650 mg was obtained, mp 165–170°, $[\alpha]^{27}D$ +53° (*c* 0.76, H_2O). Recrystallization from the same solvent mixture with a prior charcoal (Darco G-60) treatment gave a white solid. One more recrystallization, this time from *n*-BuOH–H_2O, for 3 days in the refrigerator yielded the analytical sample as clear, colorless crystals, mp 175–179° (to an extremely viscous liquid); $[\alpha]^{22}D$ +41° (*c* 0.61, H_2O); uv spectrum, $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 13,040), $\lambda_{max}^{pH\ 7}$ 259 mμ (ε 13,250), $\lambda_{max}^{pH\ 13}$ 259 mμ (ε 13,650). This material migrated as homogeneous spots on the plates,[11] R_{Ad} 1.26 in 5% aqueous Na_2HPO_4 and 0.23 in *n*-BuOH–H_2O (86:14 v/v).

Anal. Calcd for $C_{18}H_{25}N_5O_{13}$: C, 46.05; H, 5.68; N, 15.65. Found: C, 46.34; H, 5.79; N, 15.65.

An attempt was made to elucidate the configuration of this nucleoside by nmr spectroscopy,[12] but the results were not conclusive and the configuration remains undesignated.

(1) Supported by Grant No. T-442 from the American Cancer Society.

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(12) Obtained by Dr. Harry Agahigian of the Baron Consulting Co.

Quinazolines and 1,4-Benzodiazepines. XXXIX.[1] The Synthesis of Dihydroimidazo- and Tetrahydropyrimido[1,2-*a*][1,4]benzodiazepines

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Pursuant to our interest in the pharmacological activity of new 1,4-benzodiazepines[1] and specifically of aminoalkyl-substituted benzodiazepines,[2] we have prepared some tetrahydropyrimido[1,2-*a*][1,4]benzodiazepines[3,4] (**3**) (Table I) and 8-chloro-6-(2-fluorophenyl)-1,2-dihydro-4H-imidazo[1,2-*a*][1,4]benzodiazepine (**4**).

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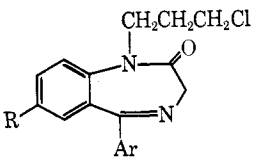
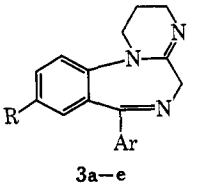
TABLE I

1-SUBSTITUTED 1,4-BENZODIAZEPINES



2a–e



3a–e

Compd	R	Ar	Method	Recrystn solvent[a]	Mp, °C	Yield, %	Formula	Analyses[b]
2a	Cl	C_6H_5	I	A-B	87–90	72.3	$C_{18}H_{16}Cl_2N_2O$	C, H
2b	Cl	*o*-FC_6H_4	I	A-B	86–89	49.5	$C_{18}H_{15}Cl_2FN_2O$	C, H
2c	Br	2-Pyridyl	I	A-C	103–106	41.9	$C_{17}H_{15}BrClN_3O$	C, H, N
2d	CF_3	C_6H_5	I	A-C	118–123	50.4	$C_{19}H_{16}ClF_3N_2O$	C, H, N
2e[c]	H	C_6H_5	I					
3a	Cl	C_6H_5	II	F-C	155–157		$C_{18}H_{16}ClN_3$	C, H, N
3a·HI				D	270–275	49.3	$C_{18}H_{16}ClN_3$·HI	C, H
3b	Cl	*o*-FC_6H_4	II	E-F	161.5–163		$C_{18}H_{15}ClFN_3$	C, H, N
3b·HI				D-A	286–289	64.7	$C_{18}H_{15}ClFN_3$·HI	C, H, N
3c	Br	2-Pyridyl	II	F	178–181		$C_{19}H_{15}BrN_4$	C, H, N
3c·HI				D	272–275	34.5	$C_{17}H_{14}BrN_4$·HI	C, H, N
3d	CF_3	C_6H_5	II	F	179–181		$C_{19}H_{16}F_3N_3$	C, H, N
3d·HI				D	278–282	38.4	$C_{19}H_{16}F_3N_3$·HI	C, H
3e	H	C_6H_5	II	A	143–145		$C_{18}H_{17}N_3$	C, H, N
3e·HI				D	293–295	52.3	$C_{18}H_{17}N_3$·HI	C, H, N

[a] A = Et_2O, B = petroleum ether (bp 30–60°), C = hexane, D = EtOH, E = C_6H_6, F = cyclohexane. [b] Acceptable analytical results were obtained for the elements indicated. [c] The isolation of this compound gave a 40.4% yield of an oil which was converted to **3e** without characterization.

Experimental Section[5]

1-(3-Chloropropyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-ones (2a–e). Method I.—The appropriate 1,4-benzodiazepin-2-one (**1a–e**)[6] was dissolved in a mixture of DMF and THF (1:1) and this solution, under dry N_2, was treated with excess (10–25%) $NaNH_2$. The mixture was stirred for 2 hr at 50° and was then treated with a threefold excess of 1-bromo-3-chloropropane and was stirred overnight. The reaction mixture was poured into ice water and extracted with CH_2Cl_2 which was dried and evaporated to dryness. The residue was chromatographed on Woelm neutral alumina (Activity 1) on which the product was always less strongly adsorbed than the starting material.

1,2,3,5-Tetrahydropyrimido[1,2-*a*][1,4]benzodiazepines (3a–e). Method II.—A mixture of the appropriate 1-(3-chloropropyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (**2a–e**), 1 equiv of KI, and excess NH_3 in EtOH was heated at 75° for 10 hr with shaking in a sealed container. The reaction mixture was filtered, removing KI, and the filtrate was concentrated *in vacuo* to a residue which was recrystallized from EtOH to give the product as the hydriodide salt. These salts were neutralized in the usual manner to give the crystalline free bases.

8-Chloro-6-(2-fluorophenyl)-1,2-dihydro-4H-imidazo[1,2-*a*][1,4]benzodiazepine (4).—A solution of 5.0 g (15 mmol) of 1-(2-aminoethyl)-7-chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one[7] in 100 ml of EtOH was heated for 24 hr at reflux. The solvent was removed *in vacuo* to give a gum which was then triturated with cyclohexane to give 3.9 g (82.5%) of crystals, mp 174–177°. Recrystallizations from CH_2Cl_2–cyclohexane gave pure product as colorless needles, mp 175–177°. *Anal.* ($C_{17}H_{13}ClFN_3$) C, H, N, Cl, F.

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(5) All melting points were determined on a hot stage microscope and are corrected.

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Some 4H,12H-Pyrano[2,3-*a*]phenoxazin-4-ones

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Derivatives of phenoxazine[2–5] and γ-pyrone[6–11] are reported to possess marked physiological activity. It was thought desirable to synthesize some 4H,12H-pyrano[2,3-*a*]phenoxazine-4-ones which will incorporate both phenoxazine and γ-pyrone moieties in its molecule, for biological evaluation.

Experimental Section[12]

8-Amino-7-hydroxy-2-methylchromone was prepared by reducing 8-nitro-7-hydroxy-2-methylchromone[13] with sodium hy-

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