TABLE I
DERIVATIVES OF SALICYLIC ACID

Compd	Name	Recrystn solvent[a]	Yield,[b] %	Mp, °C	Formula[c]
I	4-Methyl-3-pentenoylsalicylic acid	A	95	99.5–100.5	$C_{13}H_{14}O_4$
II	5-Methyl-4-hexenoylsalicylic acid	A	93	106–107	$C_{14}H_{16}O_4$
III	Geranoylsalicylic acid		89	Oil	$C_{17}H_{20}O_4$
IV	Citronelloylsalicylic acid		95	Oil	$C_{17}H_{22}O_4$
V	Homogeranoylsalicylic acid	B	90	69–70	$C_{18}H_{22}O_4$
VI	Geranylacetylsalicylic acid	B	89	70–71.5	$C_{19}H_{24}O_4$
VII	Farnesoylsalicylic acid		97	Oil	$C_{22}H_{28}O_4$
VIII	Homofarnesoylsalicylic acid		91	Oil	$C_{23}H_{30}O_4$
IX	Farnesylacetylsalicylic acid		90	Oil	$C_{24}H_{32}O_4$
X	α-Cyclogeranoylsalicylic acid	A	92	100–101	$C_{17}H_{20}O_4$

[a] A = hexane, B = petroleum ether (bp 40–70°). [b] Crude product. [c] All compounds were analyzed for C, H; the analytical values were within ±0.4% of the threoretical values.

Experimental Section[1]

General Procedure.—The acid chloride (0.06 mole) was added dropwise to an ice-cooled stirred solution of salicylic acid (0.06 mole) and pyridine (0.06 mole) in anhydrous ether (100 ml). The mixture was stirred for 15 hr at room temperature and then refluxed for 5 hr. The suspension was cooled and filtered, and the solution was washed (H_2O) and dried (Na_2SO_4). The solvent was removed *in vacuo* to give the crude product. When possible, the products were crystallized from suitable solvents.

(1) Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

Preparation and Properties of a Nitrogen Mustard Derived from Methylpyrazine[1a]

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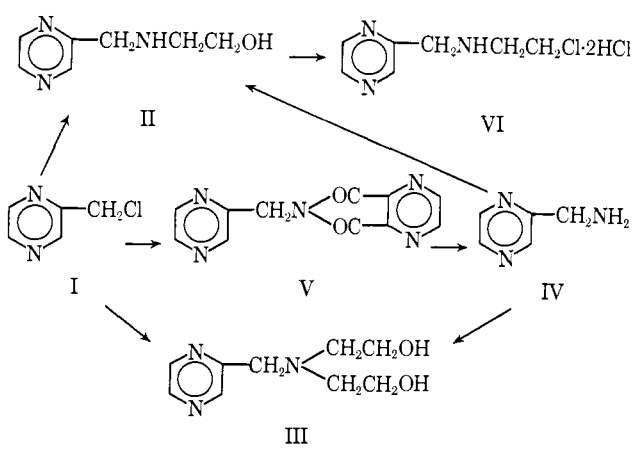
A survey of the literature of nitrogen mustards reveals that no β-chloroethylamino derivative of pyrazine or any of its alkyl derivatives has been reported. We now wish to report the synthesis of a nitrogen mustard derivative of the simple pyrazine nucleus, and the preparation of some related pyrazine derivatives as summarized in Chart I.

CHART I



(1) (a) Abstracted from a thesis submitted by Paul G. Mattner in partial fulfillment of the requirements for the M.S. degree, Long Island University, Feb 1967. (b) To whom all inquiries should be sent.

Experimental Section[2]

2-(2-Hydroxyethyl)aminomethylpyrazine (II).—A thoroughly stirred mixture of 24.7 g (0.19 mole) of α-chloromethylpyrazine (I),[3] 16.1 g (0.19 mole) of $NaHCO_3$, and 35.1 g (0.57 mole) of ethanolamine in 50 ml of 95% EtOH was allowed to reflux for 13 hr. The reaction mixture was then cooled, filtered, concentrated under vacuum, and treated with 300 ml of Me_2CO. The Me_2CO mixture was filtered and the filtrate was concentrated under vacuum. The residual oil was distilled, and the fraction boiling at 129–131° (0.5 mm) was collected. A second distillation afforded 11.07 g (39.9%) of light yellow oil boiling at 100–102° (0.1 mm). A pale yellow analytical sample was obtained by neutralization of II·2HCl (see below), which was carried out by treating a solution of 5.13 g (0.023 mole) of the dihydrochloride in 5 ml of H_2O with 10 ml of 40% NaOH and continuously extracting the resulting mixture with Et_2O for 5 days. The Et_2O extract was dried (Na_2SO_4) and concentrated under vacuum to yield 2.44 g (70%) of II, bp 98–100° (0.1 mm). *Anal.* ($C_7H_{11}N_3O$) C, H, N.

The dihydrochloride was obtained in 82% yield by treating II in MeOH with dry HCl and precipitating with Me_2CO to yield a light pink solid, mp 128–132° dec. *Anal.* ($C_7H_{13}Cl_2N_3O$) C, H, Cl, N.

2-Bis(2-hydroxyethyl)aminomethylpyrazine (III). A.—This compound was prepared in 16.5% yield following the procedure previously described for II and distilled as a deep orange viscous oil boiling at 134–136° (0.1 mm). An analytical sample was obtained by neutralizing 5.5 g (0.02 mole) of III·2HCl (see below), using the procedure as for II. The light yellow viscous oil boiled at 160–162° (0.2 mm). *Anal.* ($C_9H_{15}N_3O_2$) H; C: calcd, 54.80; found, 55.23. N: calcd, 21.31; found, 21.81.

III·2HCl melted at 131–133° dec. *Anal.* ($C_9H_{17}Cl_2N_3O_2$) C, H, Cl, N.

B.—To 4.05 g (0.027 mole) of 2-(2-hydroxyethyl)aminomethylpyrazine (II) cooled to 0° was added 1.8 g (0.040 mole) of liquid ethylene oxide. The reaction flask was sealed under positive pressure. The reaction mixture was then allowed to stand at room temperature for 23 hr. The brown oil was distilled at 146° (0.2 mm), yield 3.18 g (61%). The ir spectrum of the product was identical with that of the compound prepared in procedure A.

Pyrazinylmethylphthalimide (V).—To a boiling mixture of 15.7 g (0.084 mole) of potassium phthalimide and 45 ml of DMF was slowly added 10.9 g (0.084 mole) of I. The reaction mixture was cooled, treated with 50 ml of $CHCl_3$, and poured into 100 ml of H_2O. The aqueous phase was extracted with two 20-ml portions of $CHCl_3$. The $CHCl_3$ solution and extracts were combined, dried (Na_2SO_4), and evaporated under reduced pressure. To the residual slurry was added 400 ml of Et_2O and the resulting mixture was filtered. The solid was recrystallized from Me_2CO (carbon) to yield 6.39 g (31.5%) of V, mp 146–150°. An analytical sample was obtained by recrystallization from Me_2CO and then EtOH as a white solid, mp 154–155°. *Anal.* ($C_{13}H_9N_3O_2$) C, H, N.

(2) Ir spectra were obtained using KBr pellets on a Perkin-Elmer Infracord, Model 137D. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elelents were within ±0.4% of the theoretical values.

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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 tlc 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°, $[\alpha]^{25}D$ +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 tlc 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 $C_{17}H_{25}N_5O_{12}$: 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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