The resulting solution was neutralized with NaOH pellets and extracted with Et_2O. After drying (Na_2SO_4), the mixture was purified by column chromatography over 10 g of alumina. The pure product (0.12 g, 55%), a light yellow liquid, was eluted with Et_2O. Tlc indicated a single component with an R_f of 0.78 (Al_2O_3–Et_2O). *Anal.* ($C_{10}H_{13}ClN$) C, H, Cl.

"Complex" from the Hydrolysis of 3-Phenyl-4-methoxypyridine.—3-Phenyl-4-methoxypyridine, 30 g (0.162 mole), was refluxed for 3 hr with 200 ml of 58% HI, and the mixture was cooled and diluted with 100 ml of ice slush. Na_2SO_3 was added until the solution changed from dark red to light orange. NaOH pellets were added (with cooling) until a buffered pH of *ca.* 5 was reached. The semisolid that came out of solution was filtered off and triturated repeatedly with Et_2O to remove 6.3 g of starting methoxy compound. The residue (39 g) was a stable, colorless solid, mp 50–90°. The precise composition of this complex was not elucidated. *Anal.* Found: C, 44.3; H, 3.53; N, 4.59; I, 35.5. Upon treatment with aqueous NaOH, however, it was converted to a mixture of 4-methoxy-3-phenylpyridine and 4-hydroxy-3-phenylpyridine. Recrystallization from H_2O (low recovery) gave a solid containing 19.3% iodine.

When treated with ω-dialkylaminoalkylamines, the complex was converted to 4-dialkylaminoalkylamino-3-phenylpyridines nearly as efficiently as was 4-chloro-3-phenylpyridine. The formation of the complex, rather than the mixture of 4-methoxy- and 4-hydroxypyridines that was obtained previously, was apparently a function of the lower pH of the solution from which the complex was isolated.

4-Dialkylaminoalkylamino-3-phenylpyridines. General Procedure.—A mixture of 1 part of the 3-phenylpyridine substrate (4-chloro-3-phenylpyridine or "complex") and 2.5–5 parts of the appropriate ω-dialkylaminoalkylamine was heated in a steel bomb at 185–215° for 15–16 hr. The reaction mixture was cooled and poured into H_2O, and the crude product was isolated by Et_2O extraction. Column chromatography over alumina, using Et_2O or 5% MeOH in Et_2O as eluent, provided pure products as nearly colorless oils. Yields were best when a large excess of diamine was employed. In general, 5.0 g of complex provided between 1.3 and 4.3 g of pure free base. In the one instance where it was used (n = 3, Table I), 4-chloro-3-phenylpyridine provided an 83% yield of product.

Although not used as a preparative method, it was found in later small-scale experiments that 4-methoxy-3-phenylpyridine would serve as well as 4-chloro-3-phenylpyridine in the displacement reaction.

Oxalate salts were prepared in a pure state by adding acetone solutions (*ca.* 10%) of 2 molar equiv of oxalic acid to acetone solutions of the amines. Recrystallization was not usually necessary.

4-Amino-1-(β-D-ribofuranosyl)benzimidazole

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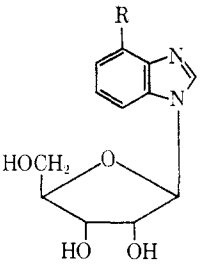
Received March 1, 1968

We recently described the synthesis of 4-amino-1-(β-D-ribofuranosyl)indole[2] as an example of a trideazaadenosine. A logical extension of this work would be the synthesis of a dideazaadenosine. From among the three possibilities, 4-amino-1-(β-D-ribofuranosyl)benzimidazole (I) was chosen because of the interesting biological properties of several benzimidazoles. 4-Nitro-1-(β-D-ribofuranosyl)benzimidazole (II) had been reported[3]



I, R = NH_2
II, R = NO_2

earlier but its conversion to the related 4-amino-1-(β-D-ribofuranosyl)benzimidazole (I) was not described. This conversion was accomplished by the hydrogenation of II in the presence of a palladium-on-carbon catalyst.

The previous[3] assignment of a β-anomeric configuration to II was confirmed through the observation that I shows a negative Cotton effect in its ORD curve. For use in comparison with I in biological testing, a sample of 4-aminobenzimidazole (III)[4] was similarly synthesized by catalytic hydrogenation of 4-nitrobenzimidazole.[5]

In cytotoxicity tests against KB cells III showed an ED_{50} at 5 μg/ml, whereas I had an ED_{50} at >100 μg/ml.[5]

Experimental Section

4-Amino-1-(β-D-ribofuranosyl)benzimidazole.—A suspension of 510 mg (1.73 mmoles) of 4-nitro-1-(β-D-ribofuranosyl)benzimidazole and 510 mg of 5% Pd-C in 125 ml of MeOH was shaken with H_2 at 3.5 kg/cm² at 25° for 30 min. The catalyst was removed and the filtrate was concentrated to about 10 ml and kept at 5° for 16 hr. A crop of crystals (314 mg, mp 86°) was removed and the filtrate was concentrated to 4 ml. A second crop of crystals (100 mg, mp 86°) was obtained. The combined crops were recrystallized from 2 ml of H_2O and the product was dried over P_2O_5 at 80° and reduced pressure for 2 hr. The yield was 320 mg (70%), mp 137–138°;[6] $[\alpha]_D$ −49°, $[\alpha]_{578}$ −52° (*c* 1, H_2O); $[\phi]_{350}$ −660°, $[\phi]_{300}$ −1640° (tr), $[\phi]_{275}$ −490° (pk), $[\phi]_{265}$ −920° (tr), $[\phi]_{255}$ 0°, $[\phi]_{254}$ +270° (pk); $\lambda_{max}^{H_2O}$ [mμ (ε × 10⁻³)] pH 1—222 (14.2), 255 (3.8), 267 (4.5), 274 (4.6), 287 (2.5); pH 7—218 (25.6), 263 (7.6), 287 (4.4); pH 13—263 (7.5), 287 (4.4); R_f 0.59, tlc on cellulose in H_2O (visualized by uv absorption and $KMnO_4$ spray); τ^{D_2O} 3.46 ppm (d, C-1′ proton, $J_{1',2'}$ = 4.8 cps).

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.33; H, 5.70; N, 15.68.

(1) To whom inquiries should be addressed.

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(5) Personal communication from Dr. C. O. Gitterman of the Merck Sharp & Dohme Research Laboratories.

(6) The melting point of 86° obtained above was probably that of a solvate of undetermined composition.

Terpene Compounds as Drugs. V. Terpenyl Derivatives of Salicylic Acid

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Received February 12, 1968

Continuing our studies in the field of terpene chemistry, we esterified salicyclic acid with terpenyl acids in order to seek possible differences from acetylsalicylic acid in analgetic and antiinflammatory activity and in a decrease of undesirable side effects. The new substances, which are listed in Table I, displayed on a whole better gastric tolerance than acetylsalicylic acid, however, at markedly decreased activity.

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	$C_{17}H_{26}O_4$

[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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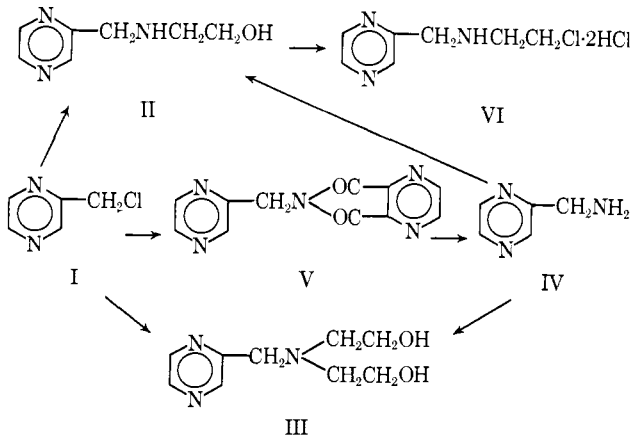
Received January 19, 1968

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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