TABLE III
6,8-DIBROMO-3-SUBSTITUTED 2-(N,N-BENZYLPHENYLCARBOXAMIDOMETHYLTHIO)-4(3H)-QUINAZOLINONES[a]

R	% yield	Mp, °C	Formula[b]
C_6H_5	70	113	$C_{29}H_{21}Br_2N_3O_2S$
o-$CH_3C_6H_4$	45	245	$C_{30}H_{23}Br_2N_3O_2S$
m-$CH_3C_6H_4$	50	84	$C_{30}H_{23}Br_2N_3O_2S$
p-$CH_3C_6H_4$	60	88	$C_{30}H_{23}Br_2N_3O_2S$
m-ClC_6H_4	65	103	$C_{29}H_{20}Br_2ClN_3O_2S$
p-ClC_6H_4	55	96	$C_{29}H_{20}Br_2ClN_3O_2S$
p-$OCH_3C_6H_4$	65	93	$C_{30}H_{23}Br_2N_3O_3S$
p-$OC_2H_5C_6H_4$	75	111	$C_{31}H_{25}Br_2N_3O_3S$
n-C_4H_9	35	219	$C_{27}H_{25}Br_2N_3O_2S$
$C_6H_5CH_2$	40	238 dec	$C_{30}H_{23}Br_2N_3O_2S$

[a] Crystallization solvent: EtOH. [b] All compounds were analyzed for Br, N. The analytical results were within ±0.3% of the calculated values.

TABLE IV
6,8-DIBROMO-3-SUBSTITUTED 2-(N,N-DIETHYLCARBOXAMIDOMETHYLTHIO)-4(3H)-QUINAZOLONES[a]

R	% yield	Mp, °C	Formula[b]
C_6H_5	60	187	$C_{20}H_{19}Br_2N_3O_2S$
o-$CH_3C_6H_4$	50	162	$C_{21}H_{21}Br_2N_3O_2S$
m-$CH_3C_6H_4$	30	275 dec	$C_{21}H_{21}Br_2N_3O_2S$
p-$CH_3C_6H_4$	55	188	$C_{21}H_{21}Br_2N_3O_2S$
m-ClC_6H_4	40	270 dec	$C_{20}H_{18}Br_2ClN_3O_2S$
p-ClC_6H_4	35	295 dec	$C_{20}H_{18}Br_2ClN_3O_2S$
p-$OCH_3C_6H_4$	45	>320	$C_{21}H_{21}Br_2N_3O_3S$
p-$OC_2H_5C_6H_4$	35	235 dec	$C_{22}H_{23}Br_2N_3O_3S$
CH_3	25	305 dec	$C_{15}H_{17}Br_2N_3O_2S$
C_2H_5	30	>320	$C_{16}H_{19}Br_2N_3O_2S$
n-C_4H_9	45	285 dec	$C_{18}H_{23}Br_2N_3O_2S$
$C_6H_5CH_2$	25	248 dec	$C_{21}H_{21}Br_2N_3O_2S$

[a] Crystallization solvent: Me_2CO–EtOH–EtOAc (3:1:1). [b] All compounds were analyzed for N, S. The analytical results were within ±0.3% of the calculated values.

TABLE V
6,8-DIBROMO-3-SUBSTITUTED 2-(N-PIPERIDINOCARBOXAMIDOMETHYLTHIO)-4(3H)-QUINAZOLINONES[a]

R	% yield	Mp, °C	Formula[b]
C_6H_5	60	240	$C_{21}H_{19}Br_2N_3O_2S$
o-$CH_3C_6H_4$	35	238 dec	$C_{22}H_{21}Br_2N_3O_2S$
m-$CH_3C_6H_4$	40	270 dec	$C_{22}H_{21}Br_2N_3O_2S$
p-$CH_3C_6H_4$	45	250 dec	$C_{22}H_{21}Br_2N_3O_2S$
m-ClC_6H_4	50	268 dec	$C_{21}H_{18}Br_2ClN_3O_2S$
p-ClC_6H_4	55	260 dec	$C_{21}H_{18}Br_2ClN_3O_2S$
p-$OCH_3C_6H_4$	65	116	$C_{22}H_{21}Br_2N_3O_3S$
p-$OC_2H_5C_6H_4$	50	290 dec	$C_{23}H_{23}Br_2N_3O_3S$
CH_3	30	280 dec	$C_{16}H_{17}Br_2N_3O_2S$
n-C_4H_9	25	305 dec	$C_{19}H_{23}Br_2N_3O_2S$
$C_6H_5CH_2$	35	275 dec	$C_{22}H_{21}Br_2N_3O_2S$

[a] Crystallization solvent: Me_2CO–EtOH (2:1). [b] All compounds were analyzed for N, S. The analytical results were within ±0.3% of the calculated values.

6,8-Dibromo-3-benzyl-2-carboxymethylthio-4(3H)-quinazolinone.—An equimolar quantity of sodium monochloroacetate was added to a 6,8-dibromo-2-thio-3-benzyl-2,4(1H,3H)-quinazolindione in EtOH–NaOH, and the mixture was shaken for 6 hr. It was acidified with HCl, the precipitate obtained was dissolved in $NaHCO_3$, filtered, and reprecipitated with HCl. The product was crystallized (EtOH); yield 60%, mp 237. *Anal.* ($C_{17}H_{12}Br_2N_2O_3S$) C, H, N, S.

6,8-Dibromo-3-phenyl-1-ethyl-2-thio-2,4(1H,3H)-quinazolinedione.—A mixture of 3,5-dibromo-N-ethylanthranilic acid (1.6 g), pyridine (0.4 g), EtOH (5 ml), and phenyl isothiocyanate (0.68 g) was refluxed at 90° for 6 hr. The crystalline product was filtered and recrystallized from C_6H_6 and EtOH mixture (3:1) to give 60% yield of the required product, white needles, mp 242°. *Anal.* ($C_{16}H_{12}Br_2N_2OS$) C, H, N.

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4-Dialkylaminoalkylamino-3-phenylpyridines[1]

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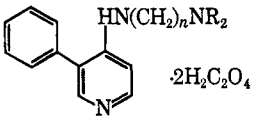
As part of a program devoted to the synthesis of novel antimalarial agents we have prepared the series of N-substituted 3-phenyl-4-aminopyridines listed in Table I. Treatment of 3-phenylpyridines bearing appropriate substituents in the 4 position with the diamines corresponding to the side chains was the general synthetic approach. The oily free bases were characterized by their nmr spectra and as oxalic acid salts. None of the tabulated compounds were active when screened against *Plasmodium berghei* in mice.[2]

TABLE I
4-DIALKYLAMINOALKYLAMINO-3-PHENYLPYRIDINE DIOXALATES



n	R	Mp, °C	Formula	Analyses[3]
2	Et	177–178	$C_{17}H_{23}N_3 \cdot 2H_2C_2O_4$	C, H, N
3	Et	155–157	$C_{18}H_{25}N_3 \cdot 2H_2C_2O_4$	C, H, N
4	Et	140–141	$C_{19}H_{27}N_3 \cdot 2H_2C_2O_4$	C, H, N
5	Et	162–164	$C_{20}H_{29}N_3 \cdot 2H_2C_2O_4$	C, H, N
6	Me	145–148	$C_{19}H_{27}N_3 \cdot 2H_2C_2O_4$	C, H, N

Experimental Section[3]

4-Methoxy-3-phenylpyridine was prepared by the procedure of Ahmad and Hey.[4] The improved Gomberg reaction procedure of Cadogan[5] was used in the final step of the sequence.

4-Hydroxy-3-phenylpyridine.—4-Methoxy-3-phenylpyridine (15 g, 81 mmoles) was refluxed for 3 hr with 100 ml of 58% HI. The solution was cooled, diluted with 80 ml of H_2O, and treated with Na_2SO_3 until the dark color had faded to orange-yellow. The solution was made slightly alkaline, and the oily solid that came out of solution was collected and washed thoroughly with Et_2O. The filtrate was extracted with Et_2O to remove unhydrolyzed starting material. From the ethereal washings and extracts was recovered 4.86 g (32%) of starting material. The remaining crystalline solid (5.3 g, 56% yield based on recovered starting material) had mp 210–225°. Recrystallization from hot H_2O gave pure product, mp 228–230°. *Anal.* ($C_{11}H_9NO$) C, H.

4-Chloro-3-phenylpyridine.—4-Hydroxy-3-phenylpyridine (0.20 g, 1.17 mmoles) was refluxed for 1.5 hr with *ca.* 2 ml of $POCl_3$; the mixture was cooled and poured into ice water.

(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This is contribution number 343 from the Army Research Program on Malaria.

(2) The antimalarial tests were performed by Dr. Leo Rane of the University of Miami [T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)]. Testing results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research.

(3) Melting points were taken in a Mel-Temp apparatus and are corrected. Microanalyses were performed by the Stanford Research Institute Analytical Laboratories. Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(4) Y. Ahmad and D. Hey, *J. Chem. Soc.*, 4516, 4521 (1954).

(5) J. Cadogan, *ibid.*, 4257 (1962).

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.* ($C_{10}H_8ClN$) 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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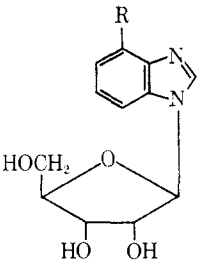
We recently described the synthesis of 4-amino-1-(β-D-ribofuranosyl)indole[2] as an example of a trideazaadenosine. A logical extension of this work would be the synthesis of a dideazaadenosine. From among the three possibilities, 4-amino-1-(β-D-ribofuranosyl)benzimidazole (I) was chosen because of the 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.

(2) E. Walton, F. W. Holly, and S. R. Jenkins, *J. Org. Chem.*, **33**, 192 (1968).

(3) Y. Mizuno, M. Ikehara, F. Isikawa, and H. Ikehara, *Chem. Pharm. Bull.* (Tokyo), **10**, 761 (1962).

(4) G. M. Vander Wani, *Rec. Trav. Chim.*, **67**, 45 (1948).

(5) Personal communication from Dr. C. O. Gilderman 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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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.