TABLE I
SULFILIMINES AND SULFOXIMINES

$$R_1SR_2(NSO_2R_3)$$

Compd	R_1	R_2	R_3	Mp,[a] °C	Formula[b]
1	p-$CH_3CONHC_6H_4$	p-$CH_3CONHC_6H_4$	p-$CH_3C_6H_4$	215–217[c]	$C_{23}H_{23}O_4N_3S_2$
2	p-$CH_3CONHC_6H_4$	p-$CH_3CONHC_6H_4$	C_6H_5	205[d]	$C_{22}H_{21}O_4N_3S_2$
3	p-$NH_2C_6H_4$	p-$NH_2C_6H_4$	C_6H_5	197[e]	$C_{18}H_{17}O_2N_3S_2$
4	p-$NH_2C_6H_4$	p-$NH_2C_6H_4$	p-$CH_3C_6H_4$	230[e]	$C_{19}H_{19}O_2N_3S_2$
5	p-$NH_2C_6H_4$	CH_3	C_6H_5	167[c]	$C_{13}H_{14}O_2N_2S_2$
6	p-$NH_2C_6H_4$	p-$NH_2C_6H_4$	p-NH_2C_6H	245 dec[e]	$C_{18}H_{18}O_2N_4S_2$
7[f]	p-$CH_3CONHC_6H_4$	p-$CH_3CONHC_6H_4$	p-$CH_3CONHC_6H_4$	163[c]	$C_{24}H_{24}O_5N_4S_2 \cdot H_2O$
8	p-$CH_3CONHC_6H_4$	CH_3	C_6H_5	162[c]	$C_{15}H_{16}O_3N_2S_2$
9	p-$NH_2C_6H_4$	CH_3	p-$CH_3C_6H_4$	212 dec[c]	$C_{14}H_{16}O_2N_2S_2$
10	p-$CH_3CONHC_6H_4$	CH_3	p-$CH_3C_6H_4$	185[c]	$C_{16}H_{18}O_3N_2S_2$
11	p-$CH_3CONHC_6H_4$	CH_3	p-$CH_3CONHC_6H_4$	215 dec[g]	$C_{17}H_{19}O_4N_3S_2$
12	p-$NH_2C_6H_4$	CH_3	p-$NH_2C_6H_4$	224 dec[h]	$C_{13}H_{13}O_2N_3S_2$
13	p-$CH_3CONHC_6H_4$	6-(3-Acetylamino-4-pyridyl	C_6H_5	242[e]	$C_{21}H_{20}O_4N_4S_2$
14	p-$CH_3CONHC_6H_4$	6-(3-Acetylamino)-pyridyl	p-$CH_3C_6H_4$	177[d]	$C_{22}H_{22}O_4N_4S_2$
15	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$	C_6H_5	91[h]	$C_{20}H_{19}O_2NS_2$

$$R_1SOR_2(NSO_2R_3)$$

16	p-$CH_3CONHC_6H_4$	CH_3	C_6H_5	173[e]	$C_{15}H_{16}O_4N_2S_2$
17	p-$CH_3CONHC_6H_4$	CH_3	p-$CH_3CONHC_6H_4$	274[e]	$C_{17}H_{17}O_5N_3S_2$

[a] Melting points are uncorrected. [b] All new compounds analyzed satisfactorily for C, H, N, and S. Compounds **14** and **15** are not analyzed for S. [c] From MeOH. [d] From acetone. [e] From EtOH. [f] From MeOH-Me_2CO. [g] From dioxane-H_2O. [h] From $CHCl_3$. [i] Previously prepared: C. W. Todd, J. H. Fletcher, and D. S. Tarbell, *J. Amer. Chem. Soc.*, **65**, 350 (1943).

tated. The solid was recrystd from EtOH: 5.5 g; 43%; mp 274°.

Pharmacology.—All the compounds were screened against *Plasmodium gallinaceum* in mosquitoes (*Aedes aegypti*). All the compounds except **5**, **15**, and **17** were screened against *P. berghei* in mice. Compounds **12** and **15** were also screened against *P. gallinaceum* in chicks. Compound **12** showed slight activity in the mouse test. At a dose level of 320 mg/kg, the mean survival time of the treated mice was 11.6 days and at a dose level of 640 mg/kg, it was 12.8 days. The mean survival time of the control mice was 6.1 days. Compound **1** was assayed for antifolic acid activity in a bacterial system. It gave questionable activity with *Streptococcus fecalis*, but was inactive with *Lactobacillus casei* and *Pediococcus cerevisiae*. None of the other compounds showed any significant activity. All of the tests were carried out by contractors of the Walter Reed Army Institute of Research.

Acknowledgment.—This work was supported by the U. S. Army Medical Research and Development Command under Research Contract No. 49-193-MD-2946. This is Contribution No. 753 from the Army Research Program on Malaria.

Synthesis and Antimalarial Activity of 4-Aminobenzo[*b*]-1,5-naphthyridines[1]

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Received February 6, 1970

Antimalarial activity has been reported for several aminosubstituted members of the 1,5-naphthyridine[2] and 1,7-naphthyridine[3] families. Much of the rationale for the early synthetic efforts in these series was predicated on the assumption that certain aminonaphthyridines could be regarded as isosteric analogs of both 4- and 8-aminoquinolines—well-known as antimalarial agents.[4]

Although general synthetic pathways to benzo[*b*]-1,5-naphthyridines have been established,[5] no aminosubstituted antimalarial candidates appear to have been prepared or screened. The 3-aminoquinolines, synthetic precursors of this benzonaphthyridine system, are converted by reaction with ethoxymethylenemalonic ester[6] (EMME) into the 3-carbethoxy-4-hydroxy-[*b*]-1,5-naphthyridines which are modified by standard methods (*vide infra*) into 4-chlorobenzo[*b*]-1,5-naphthyridines (**1**). The cycle formation of 3-aminoquinolines and EMME occurs at C-2 of the original quinoline, leading to benzo[*b*]-1,5-naphthyridines and not at C-4 to produce isomeric benzo[*f*]-1,7-naphthyridines.[5]

Since, of several side-chain amines studied in aminoquinolines, the 3-diethylaminomethyl-4-hydroxyanilino derivatives displayed the most impressive activity,[7,8] attempts were made to incorporate it into these benzonaphthyridines by Burckhalter's procedure.[9] 4-(3-*N*,*N*-Diethylaminomethyl-4-hydroxyanilino)benzo-[*b*]-1,5-naphthyridine (**2a**) was successfully prepared from **1a** but similar attempts to aminate **1b** with the

(1) Supported by Contract DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command. This publication represents contribution No. 773 from the Army Research Program on Malaria.

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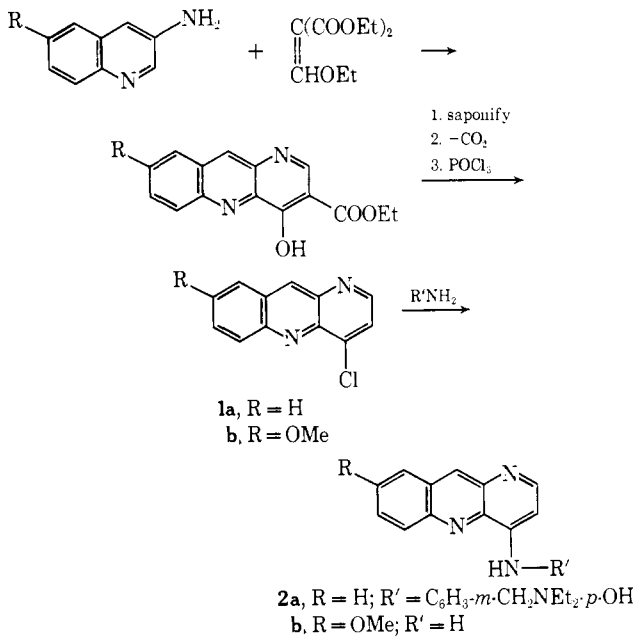

same cresol amine moiety produced only tars. The adamantylamino group has been condensed onto active halo–carbon seats,[10] but it could not be successfully made to react with **1a**. Only the 4-phenoxy material, a product of reaction with the phenol solvent, was obtained. NH_3 in hot phenol, however, provided a 41% yield of the 4-amino-8-methoxybenzo[*b*]-1,5-naphthyridine (**2b**) from the corresponding chloro compound.

Biological Activity.[11]—Compounds **1a**, **1b**, **2a**, **2b**, **3**, **4**, and **5** were tested by the Gerberg procedure on a standard strain of *Aedes aegypti* mosquito infected with *Plasmodium gallinaceum*. Compound evaluation was based on the ability of the chemical to suppress the development of malarial oocysts in the midgut or to suppress the number of sporozoites in the salivary gland of the mosquito. No suppression was observed with any of the test compounds. In addition **1b**, **3**, **4**, and **5** were screened against blood-induced *P. gallinaceium* infection in white Leghorn cockerel chicks and against *P. berghei* in mice. Although the compounds were nontoxic to the host animal at doses as high as 640 mg/kg in the mouse and 120 mg/kg in the chick, they were similarly nontoxic to the parasite and displayed no antimalarial activity.

Experimental Section[12]

4-Chlorobenzo[*b*]-1,5-naphthyridine (**1a**).—A mixture of 3.1 g (11 mmol) of 3-carbethoxy-4-hydroxybenzo[*b*]-1,5-naphthyridine[5] and 40 ml of 10% aq NaOH was refluxed for 45 min., treated with charcoal, filtered, and neutralized with dil HCl. The precipitated acid, after vacuum drying, was added portionwise to 50 ml of boiling Ph_2O, refluxed 0.5 hr, cooled, dild with petr ether (bp 60–110°) and the 4-hydroxybenzo[*g*-1,5]naphthyridine (1.7 g) collected. Treatment of the 4-OH compound with 2.0 ml of $POCl_3$ at reflux for 10 min converted it into **1a**. The product was isolated by pouring the $POCl_3$ solution onto ice containing a slight excess of concd NH_4OH, and extracting (Et_2O). The dried ($MgSO_4$) ether yielded **1a** as a green powder upon evaporation. Sublimation at 90° (1 Torr) gave 0.89 g (39%), mp 115.5–117°. *Anal.* ($C_{12}H_7ClN_2$) C, H, N.

4-(3-*N*,*N*-Diethylaminomethyl-4-hydroxyanilino)benzo[*b*]-1,5-naphthyridine (**2a**).—A solution of 321 mg (1.36 mmol) of *p*-acetamido-α-diethylamino-*o*-cresol in 0.68 ml of 18% aq HCl was refluxed 1 hr, neutralized to pH 6 with 50% NaOH, and treated with 1.36 mmol of **1a** in 3 ml of DMF.[13] This mixture was heated on a steam bath for 36 hr, cooled, poured into H_2O, and made basic with NaOH. The precipitated solid was taken up in $CHCl_3$, washed with 10% NaOH, dried ($MgSO_4$), and the solvent removed *in vacuo*. The resulting crystals (62%) were purified by recrystallization from MeOH–H_2O, mp 167–169°. *Anal.* ($C_{23}H_{24}N_4O$) C, H, N.

Attempted Preparation of 4-Adamantylaminobenzo[*b*]-1,5-naphthyridine.—A mixture of 0.31 g of **1a**, 0.23 g of adamantylamine, and 4.10 g of phenol was heated at 180° for 14 hr. The cooled solution when poured into 10% aqueous NaOH precipitated a solid which was dried and sublimed to give 30% of 4-phenoxybenzo[*g*-1,5]naphthyridine, mp 170–173°. *Anal.* ($C_{18}H_{12}N_2O$) C, H.

3-Carbethoxy-6-methoxyquinoline (**3**).—A mixture of 12.0 g of 3-carbethoxy-4-chloro-6-methoxyquinoline[14] (45 mmol), 200 ml of AcOH, and 3.0 g of 10% Pd–C was shaken in a Parr apparatus at 3 atm of H_2 until uptake ceased. The catalyst was filtered off, the filtrate evaporated to dryness, the crystalline hydrochloride dissolved in aqueous NaOH (pH 10), and extracted into $CHCl_3$. The dried ($MgSO_4$) $CHCl_3$ was removed *in vacuo* and the product, 7.2 g, 69%, recrystallized from petr ether (bp 60–110°) to yield light tan plates, mp 81–83°. *Anal.* ($C_{13}H_{13}NO_3$) C, H, N.

Ethyl 6-Methoxy-3-quinolylurethan (**4**).—The ester **3** saponified by standard methods yielded 35.2 g of acid which was chlorinated by 1-hr reflux in 90 ml of $SOCl_2$. After excess $SOCl_2$ was distilled off, the granular acid chloride was digested to a fine powder by refluxing in dry Me_2CO (425 ml). This suspension was chilled to 5° and added portionwise to 95 ml of H_2O containing 29 g of NaN_3 also being maintained at 5°. After 0.5 hr, the medium was diluted with 1300 ml of H_2O and the 3-carbonyl azide (85%) collected; crude material, mp 104–105°. The 33.5 g of azide and 750 ml of EtOH were refluxed for 2 hr, Norit A was added, and 400 ml of solvent were removed by distillation. The hot solution was filtered, and upon chilling of the clarified filtrate 31.0 g (86%) of white microneedles of 4 precipitated, mp from EtOH, 182–186°. *Anal.* ($C_{13}H_{14}N_2O_3$) C, H, N.

3-Amino-6-methoxyquinoline (**5**).—The urethane 4 (28.8 g, 0.117 mol) intimately mixed with 20.0 g (0.135 mol) of phthalic anhydride was converted into the phthalimido derivative by fusion at 220–230° for 0.5 hr. The crude crystalline mass was triturated thoroughly with 10% aqueous Na_2CO_3 and then with hot EtOH to yield 34.1 g (96%) of the tan phthalimido product, mp 234–237°. A mixture of the entire quantity of the phthalimido compound and 0.12 mol of 85% hydrazine hydrate in 250 ml of EtOH was stirred at reflux for 2 hr, 150 ml of 5% aqueous HCl was added, reflux was continued for 1 hr, and the mixture was filtered while hot to isolate the insoluble phthalhydrazide. Evaporation of solvent from the filtrate precipitated the hydrochloride of the desired amine which was taken up in H_2O and made strongly basic with 10% aq NaOH. The amine was extracted into a $CHCl_3$ phase which was dried ($MgSO_4$) and evaporated to yield 17.1 g (88%) of the base, mp 114–117°. The analytical sample was prepared by sublimation, white plates, mp 118–125°. *Anal.* ($C_{10}H_{10}N_2O$) C, H, N.

4-Chloro-8-methoxybenzo[*b*]-1,5-naphthyridine (**1b**).—The 3-amino-6-methoxyquinoline **5**, (15.1 g, 86 mmol) was treated with ethoxymethylenemalonic ester (48.4 g, 0.22 mol) in 400 ml of refluxing Ph_2O and was converted by the standard Gould–Jacobs technique[6] to an 82% yield of crude 3-carbethoxy-4-hydroxy-8-methoxybenzo[*b*]-1,5-naphthyridine, mp 237–248° dec. This crude ester was converted by the saponification–decarboxylation

(10) S. F. Zakrzewski, A. Bloch, and C. A. Nichol, *J. Med. Chem.*, **11**, 885 (1968).

(11) Mouse and chick screening were performed according to the standard profile described in T. S. Osdene, P. D. Russell, and L. Rane, *ibid.*, **10**, 431 (1967).

(12) Melting points were determined in a Mel-Temp apparatus and are uncalibrated. Where analyses are indicated by the symbols of the elements, analytical results are within ±0.4% of theoretical values.

(13) The presence of DMF appears to enhance yields by promoting homogeneity of the medium but an excess of DMF or elevated temperatures should be avoided for dimethylamination at C-4 often results; see N. D. Heindel and P. D. Kennewell, *Chem. Commun.*, 38 (1969), and *J. Med. Chem.*, **13**, 166 (1970).

(14) The synthesis of this compound is reported in undefined yield by $POCl_3$–PCl_5 treatment of 3-carbethoxy-4-hydroxy-6-methoxyquinoline [W. O. Kermack and N. E. Storey, *J. Chem. Soc.*, 1389 (1951)]. We have found that the PCl_5 is superfluous and that a 90% yield, mp 90.5–91.5°, can be obtained by the standard $POCl_3$ chlorination.

method described above to an 85% yield of 4-hydroxy-8-methoxybenzo[*b*]-1,5-naphthyridine, no distinct melting point but carbonization between 280 and 285°. The 4-chloro compound **1b** was prepared by refluxing 15 ml of $POCl_3$ with 13.7 g (0.609 mol) of the hydroxybenzonaphthyridine for 0.5 hr, pouring the mixture onto 1000 g of ice–100 ml of concd aq NH_4OH, and extracting thoroughly with $CHCl_3$. Evaporation of the dried ($MgSO_4$) $CHCl_3$ phase and recrystallization from petr ether (bp 60–110°) yielded the crude product, 6.1 g or 41%. An analytical sample, mp 151.5–153.0°, was prepared by vacuum sublimination. *Anal.* ($C_{13}H_9ClN_2O$) C, H, N.

4-Amino-8-methoxybenzo[*b*]-1,5-naphthyridine (2b).—A fused mixture of 4-chloro-8-methoxybenzo[*b*]-1,5-naphthyridine (1.0 g or 4.0 mmol) and 21 g of phenol maintained for 7 hr at 170–180° in an oil bath was subjected to ammonolysis by a steady stream of anhyd NH_3 introduced by a gas bubbler just below the surface of the melt. The mixture was cooled, poured into 150 ml of 10% aq NaOH, and after standing for 12 hr the crude product was collected by filtration (368 mg, 41%). Recrystallization from C_6H_6 gave light olive crystals, mp 198–201°. *Anal.* ($C_{13}H_{11}N_3O$) C, H, N.

Synthesis and Antineoplastic Evaluation of Some 9-Substituted Acridines

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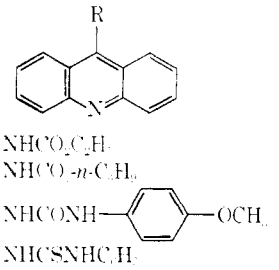
Received February 24, 1970

Interest in this laboratory in the use of acridines as potential analytical reagents resulted in the synthesis of some 9-substituted acridines, *i.e.*, carbamic acid esters (I), urea (II), and thiourea (III) compounds. Antitumor activity has been shown with some acridine derivatives,[1-6] but no clinically useful agent has yet been found.[7] A search of the scientific literature revealed that no information was available concerning possible antineoplastic activity of acridine derivatives of the I, II, and/or III types. The carbamate and urea derivatives described herein were of special interest since substituted carbamates and ureas have been shown to exhibit antineoplastic activity.[8-11]

The synthesis of the ethyl (Ia) and *n*-butyl (Ib) esters of 9-acridinecarbamic acid from 9-acridinecarboxylic acid amide has been reported previously,[12] but it involves a multistep procedure employing a starting material that is not readily available. We have made improvements in the synthetic procedure which can be seen in the Experimental Section. The esters are now obtained in one-step reactions with high yields. Furthermore, the starting material, 9-aminoacridine, is commercially available.



Compounds II and III[13] have not been reported previously. Synthetic steps leading to these compounds are described in the Experimental Section.

Screening Results.[14]—Compounds Ia, Ib, II, and III were evaluated for potential antineoplastic activity against a L-1210 lymphoid leukemia screen using mice as the host. None of the compounds tested possessed antileukemia activity in mice. High toxicity at the 400 mg/kg level was observed for Ia and III, but little or no toxicity was observed at this level for Ib and II. Thd dosage of Ia and III was subsequently reduced to 150 and 75 mg/kg, respectively, for evaluation. At dosages of 400 mg/kg for Ib and II, 150 mg/kg for Ia, and 75 mg/kg for III, the compounds were shown to be nontoxic and inactive against the leukemia screen employed.

Experimental Section[15]

9-Acridinecarbamic Acid Esters (Ia,Ib).—9-Aminoacridine (0.02 mol) and 0.02 mol of the necessary chloroformate ester were refluxed for 1 hr in 50 ml of Me_2CO in the presence of 2 g of $NaHCO_3$. The hot suspension was filtered followed by evaporation of the Me_2CO to yield a residue, which was recrystallized from EtOH–H_2O to give a yellow solid in 92% yields: Ia, mp 192–193° (lit.,[14] mp 193°); Ib, mp 147–148° (lit.,[14] mp 147°).

1-(9-Acridinyl)-3-(*p*-methoxyphenyl)urea (II).—9-Aminoacridine (0.02 mol) and 0.02 mol of *p*-methoxyphenyl isocyanate were refluxed for 30 min in 50 ml of Me_2CO. The Me_2CO was evaporated to give a residue, which was recrystallized from EtOH–H_2O to yield a yellow solid, mp 228–229°, in 95% yield. *Anal.* ($C_{21}H_{17}N_3O_2$) C, H, N.

1-(9-Acridinyl)-3-phenyl-2-thiourea (III) was prepared according to the same procedure as II except that phenyl isothiocyanate was employed. A yellow solid, mp 189–191°, was obtained in 95% yield. *Anal.* ($C_{20}H_{15}N_3S$) C, H, N.

Acknowledgment.—This research was supported in part by the Office of General Research, University of Georgia. We wish to thank Dr. H. B. Wood, Jr., of the Cancer Chemotherapy National Service Center for the antineoplastic screening data.

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(14) The tests for antineoplastic activity were carried out by the Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda, Md.
(15) Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ± 0.4% of the theoretical values. Melting points were taken in capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were obtained from Galbraith Laboratories, Knoxville, Tenn. Ir spectra were recorded on a Perkin-Elmer Model 237 B spectrophotometer and were as expected.