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 sublimation. *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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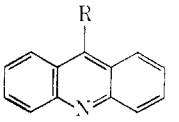
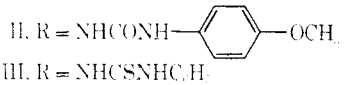
Interest in this laboratory in the use of acridines as potential analytical reagents resulted in the synthesis of some 9-substituted acridines, *i.e.*, carbamic acid esters (I), urea (II), and thiourea (III) compounds. Antitumor activity has been shown with some acridine derivatives,[1-6] but no clinically 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



Ia, R = $NHCO_2C_2H_5$
b, R = $NHCO_2$-*n*-C_4H_9



II, R = $NHCONH$—C₆H₄—OCH_3

III, R = $NHCSNHC_6H_5$

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.

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(13) III has been synthesized concurrently with this research by Dr. D. Hong, College of Pharmacy, University of Michigan, by treating 9-isothiocyanatoacridine with aniline.
(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.