the cyclopropylmethyl group as these undergo reductive ring opening under hydrogenation conditions.§

The methods outlined above should prove to be of use in other series of compounds in which similar enamines can be generated and isolated, *e.g.*, meperidine and its analogs,[9] dihydromorphines,[10] morphinans, and benzomorphans,[11] provided such compounds contain no functional groups reactive toward both catalytic hydrogenation and borohydride reduction.

Experimental Section

Specific activities were determined in a Packard Tricarb 3003 scintillation spectrometer. Samples were counted in a cocktail containing naphthalene (100 g), 2,5-diphenyloxazole (5.0 g), and 1,4-bis[2-(5-phenyl)oxazolyl]benzene (0.05 g) in 1,4-dioxane (1000 ml). Chemical and radiochemical purities were estimated by tlc on Kieselgel 60 F_{254} plates (5 × 20 cm) supplied by Merck Ag using the following solvent systems: (i) *n*-BuOH-AcOH-H_2O (20:5:8), (ii) $CHCl_3$-MeOH-H_2O (8:5:1), (iii) EtOAc-MeOH (75:25). Distribution of radioactivity on the plates was determined with a Tracerlab 4π scanner. Radiochemical starting materials were supplied by the Radiochemical Centre, Amersham, England. Experimental details are given for etorphine only. Other compounds were labeled in an analogous manner.

15,16-Didehydrooripavine Derivatives. 15,16-Didehydrooripavine derivatives were prepared from the parent tertiary bases by the method of Lewis, *et al.*[5]

6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylbutyl)tetrahydro-[15-^{3}H]oripavine ([15-^{3}H]Etorphine). 2a (100 mg, 0.24 mmol) was placed in a round-bottomed flask (25 ml) attached to a vacuum bridge. ^3H_2O (*ca.* 20 Ci, 80 μl) was frozen in liquid nitrogen, dry dioxane (3 ml) added, and the mixture vacuum transferred to the reaction flask. The vacuum was released to allow the addition of $NaBH_4$ (150 mg, 3.9 mmol). The reaction mixture was stirred at ambient temperature for 2 hr and taken to dryness *in vacuo*, and K_2CO_3 (0.5 g) in H_2O (3 ml) and dioxane (3 ml) was added. The mixture was heated at 90° for 10 min and cooled, and the volatile materials were again removed *in vacuo*. H_2O (5 ml) was added and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed repeatedly with H_2O, dried (Na_2SO_4), and taken to dryness to yield the crude product (60 mg). A portion of this material (14 mg) was chromatographed on a silica column (30 × 1 cm; Merck Ag Kieselgel 60, 0.063–0.200 mm) with Et_2O as eluent. Fractions which contained only the required product were united and treated with a little ethereal HCl to yield [15-^{3}H]etorphine hydrochloride (6 mg, 16%): sp act. 260 mCi/mmol; radiochemical purity >98%.

6,14-*endo*-Etheno-7α-(1-hydroxy-1-methylbutyl)tetrahydro-[15,16-^{3}H]oripavine ([15,16-^{3}H]Etorphine). Method a. [15,16-^{3}H]-Etorphine was synthesized by a route analogous to the method used for the 15-^{3}H derivative, NaB^3H_4 being used in the reduction step: sp act. 900 mCi/mmol; radiochemical purity of product >98%.

Method b. 2a (25 mg, 0.06 mmol) and 10% palladized charcoal (10 mg) in ethyl acetate (3 ml) was placed in a flask connected by a vacuum bridge to a break-seal ampoule containing $^3H_2$ gas (*ca.* 10 Ci; 4 ml at STP). The solution was cooled in liquid nitrogen and the system was evacuated and closed. The reaction mixture was exposed to $^3H_2$ gas by breaking the ampoule seal. The flask was allowed to warm to room temperature and the mixture stirred for 2 days, after which time hydrogen was introduced *via* the bridge to restore atmospheric pressure and the reaction was continued for a further 18 hr. The system was thoroughly evacuated, the catalyst removed by filtration, and the resulting solution was taken to dryness *in vacuo*. The crude product was chromatographed on a silica plate (20 × 20 × 0.2 cm) with *n*-BuOH-H_2O-AcOH (20:8:5) as eluent. The band corresponding to **1a** was eluted with CH_3OH (20 ml) and the resulting solution taken to dryness *in vacuo*. The residue was dissolved in cold 0.1 *N* HCl (5 ml) and the aqueous solution rapidly basified (K_2CO_3) and extracted with $CHCl_3$ (3 × 5 ml). The united $CHCl_3$ extracts were washed several times with water, dried (Na_2SO_4), and taken to dryness and the residue was dissolved in dry Et_2O (5 ml). Carrier **1a** (30 mg) was added and the solution was treated with a few drops of anhydrous ethereal HCl to yield [15,16-^{3}H]etorphine hydrochloride (45.8 mg, 48%): sp act. *ca.* 3.6 Ci/mmol; radiochemical purity >98%.

§H. P. Crocker, unpublished results.

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Synthesis and Biological Activity of 2′-Amino-2′-deoxy-5-fluorouridine

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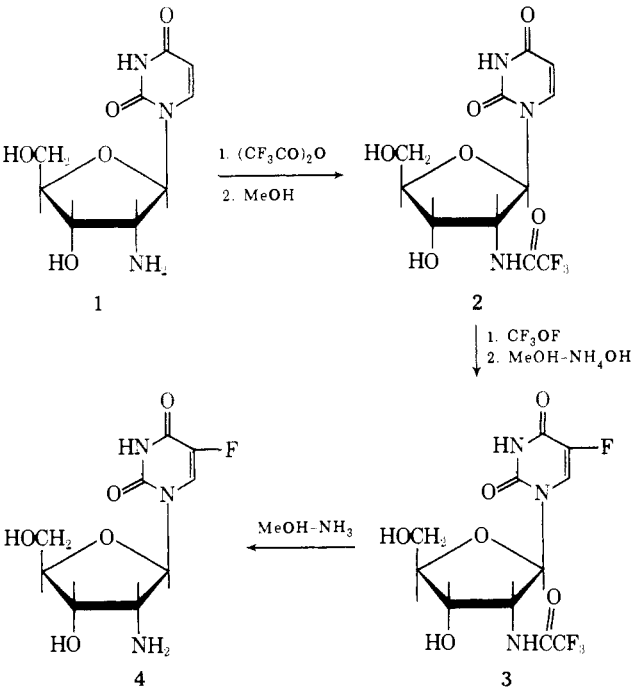
Recently, Verheyden, Wagner, and Moffatt[1] reported a useful synthesis of 2′-amino-2′-deoxyuridine and of its 5-iodo derivative. Although no information on the biological activity of these compounds has been published, it appeared worthwhile to us to prepare the 5-fluoro derivative of 2′-amino-2′-deoxyuridine, in view of the potent biological activity of other fluorinated pyrimidines.[2]



Chemical Results. Preparation of 2′-amino-2′-deoxy-5-fluorouridine (4) was first attempted by direct fluorination of 2′-amino-2′-deoxyuridine (1) with trifluoromethyl hypofluorite (CF_3OF), according to the methods described

Table I. Effect of 2′-Amino-2′-deoxy-5-fluorouridine and Some Related Compounds on the *in Vitro* Growth of Various Cell Systems

Compound	Molar concentration for 50% growth inhibition of			
	Leukemia L-1210	*E. coli* K_{12}	*S. faecium*	*S. faecium* resistant to 1 × 10^{-3} *M* 5-fluorouracil, 5-fluorouridine, and 2′-deoxy-5-fluorouridine
2′-Amino-2′-deoxy-5-fluorouridine	8×10^{-6}	6×10^{-8}	8×10^{-9}	5×10^{-7}
2′-Trifluoroacetamido-2′-deoxy-5-fluorouridine	6×10^{-5}	2×10^{-7}	1×10^{-11}	2×10^{-9}
2′-Amino-2′-deoxyuridine	$>10^{-4}$	1×10^{-7}	8×10^{-6}	2×10^{-5}
2′-Trifluoroacetamido-2′-deoxyuridine	9×10^{-5}	9×10^{-7}	2×10^{-6}	3×10^{-6}
5-Fluorouridine	5×10^{-9}	4×10^{-9}	4×10^{-11}	$>10^{-3}$
2′-Deoxy-5-fluorouridine	3×10^{-9}	5×10^{-9}	1×10^{-11}	$>10^{-3}$
Trifluoroacetic acid	2×10^{-4}	4×10^{-4}	4×10^{-4}	

by Robins and Naik[3,4] and by Barton, *et al.*[5] Under these conditions a mixture of products was obtained. Therefore, the amino function of **1** was first protected with the trifluoroacetyl group, by treating **1** with $(CF_3CO)_2O$ and removing the *O*-trifluoroacetyl groups with methanol containing a few drops of concentrated ammonium hydroxide. The resulting 2′-trifluoroacetamido-2′-deoxyuridine (**2**) was treated with CF_3OF, and the adduct was decomposed with methanol–concentrated ammonium hydroxide to yield 2′-trifluoroacetamido-2′-deoxy-5-fluorouridine (**3**). Treatment of **3** with $MeOH–NH_3$ afforded the target compound **4**.

Biological Results. The inhibitory activity of the newly synthesized compounds exerted against various *in vitro* cell systems is shown in Table I. The 5-fluoro derivative of 2′-amino-2′-deoxyuridine was found to be markedly more active than the parent compound itself. Of interest is the finding that the 2′-trifluoroacetamido derivatives of both 2′-amino-2′-deoxyuridine and 2′-amino-2′-deoxy-5-fluorouridine were more potent inhibitors of the growth of *Streptococcus faecium* cells than were the unsubstituted compounds. Indeed, 2′-trifluoroacetamido-2′-deoxy-5-fluorouridine was approximately 1000 times more active than the corresponding 2′-amino analog and was as active as 2′ deoxy-5-fluorouridine. This fact cannot, however, be interpreted to mean that substitution with the trifluoroacetyl group enhances the susceptibility of the nucleoside to cleavage of its glycosidic bond. Both 2′-trifluoroacetamido-2′-deoxy-5-fluorouridine and 2′-amino-2′-deoxy-5-fluorouridine retained pronounced activity against strains of the organism resistant to 10^{-3} *M* concentrations of 5-fluorouracil or its nucleosides. Neither is the increased activity attributable to the release of trifluoroacetic acid, since that compound is active only at about 10^{-4} *M*. In analogy, 2′-trifluoroacetamido-2′-deoxyuridine was more inhibitory of the *S. faecium* system than was 2′-amino-2′-deoxyuridine, and since, in this case, enhanced cleavage of the glycosidic bond would give rise to the metabolite uracil, the increased activity appears to be an intrinsic property of the trifluoroacetyl-substituted compound itself and suggests that it may be worth exploring the biological effects of other substituents on the 2′-amino group.

While the site of action of the newly prepared compounds remains to be determined, they appear to act as pyrimidine antimetabolites, as determined by inhibition analyses carried out with *S. faecium*. Thymidine and thymine prevented the growth inhibition exerted by the analogs most effectively, followed, in decreasing order, by deoxyuridine, uridine, uracil, deoxycytidine, cytidine, and cytosine. For instance, the inhibition indices ([I]/[S] for 50% growth) obtained with these metabolites in combination with 2′-amino-2′-deoxy-5-fluorouridine were respectively 8, 0.7, 0.08, 0.06, 0.02, 0.007, 0.003, and 0.0009, suggesting some interference of the compound along the biosynthetic path leading to the formation of DNA.

Experimental Section†

2′-Trifluoroacetamido-2′-deoxyuridine (2). 1 (1.22 g, 0.005 mol) was suspended in 100 ml of dry CH_2Cl_2 containing 2.5 ml of pyridine and was cooled in ice–water. To this suspension 5 ml of $(CF_3CO)_2O$ in 25 ml of CH_2Cl_2 was added dropwise over a period of 15 min, and stirring was continued for an additional 2 hr at room temperature. The reaction mixture was evaporated to dryness, dissolved in 150 ml of MeOH containing a few drops of concentrated NH_4OH, and stirred for 15 min. The solution was evaporated to a syrup, which was then purified on a dry silica gel column using EtOAc as the eluent. The final purification was carried out by recrystallization from MeOH–EtOAc to yield 1.33 g (78%) of **2** as colorless crystals: mp 213–214°; λ_{max} (MeOH) 258 nm (ϵ 9831); mass spectrum *m/e* 112, 113 (b + H, RI 100, b + 2 H, RI 17.0), 250 [M − 89 (ion d), RI 1.1],[6] 321 (M − H_2O, RI 1.1). *Anal.* ($C_{11}H_{12}F_3N_3O_6$) C, H, N, F.

2′-Trifluoroacetamido-2′-deoxy-5-fluorouridine (3). **2** (1.02 g, 0.003 mol) was dissolved in 50 ml of MeOH, and after addition of 150 ml of dry CH_2Cl_2, the solution was cooled to −78°. A slow stream of CF_3OF was bubbled intermittently to the magnetically stirred solution. The progress of the reaction was monitored by the disappearance of the uv-absorbing peak in the 250–300-nm region. The reaction was completed in 25–30 min. The solvent and the excess of the reagent were removed *in vacuo* at room temperature, and the remaining adduct was dissolved in 100 ml of cold MeOH containing 1 ml of concentrated NH_4OH. The solution was allowed to stand at room temperature with stirring for 16 hr, and it was then evaporated to a small volume. The product was purified by passing the residue through a dry silica gel column with EtOAc as the eluent. Further purification by recrystallization from MeOH–EtOAc afforded **3** as colorless crystals: yield 0.65 g (60%); mp 246–247°; λ_{max} (MeOH) 268 nm (ϵ 8568); mass spectrum *m/e* 130, 131 (b + H, RI 100, b + 2 H, RI 31.4), 268 [M − 89 (ion d), RI 1.4], 321 (M − $2H_2O$, RI 0.7). *Anal.* ($C_{11}H_{11}F_4N_3O_6$) C, H, N, F.

2′-Amino-2′-deoxy-5-fluorouridine (4). **3** (400 mg) was dissolved in 100 ml of MeOH saturated at 0° with ammonia. The solution was kept at room temperature with stirring for 40 hr and was then evaporated to a colorless syrup. This syrup was dissolved in absolute EtOH, and the product was precipitated with ether. After cooling overnight, it was filtered and washed with

† Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Uv spectra were recorded on a Cary Model 14 spectrophotometer. The mass spectra were recorded on a CEC21-491 double focusing mass spectrometer using an ionization voltage of 70 eV. Satisfactory analyses (C, H, N, F, within ±0.3% of the theoretical values) were obtained from Robertson Laboratory, Florham Park, N. J. Evaporations were carried out under reduced pressure in a rotary evaporator.

ether to furnish 4 as a colorless crystalline material, yield 233 mg (80%), which on tlc with (n-BuOH–H_2O 86:14) gave a single spot. To eliminate the possible presence of even traces of 5-fluorouracil which would interfere with the biological assay of the compound, further purification was carried out on prewashed 3-mm paper using the same solvent: mp 155–157°; λ_{max} (MeOH) 268 nm (ϵ 7699); mass spectrum m/e 130, 131 (b + H, RI 100, b + 2 H, RI 7.4), 154 (M − 107, RI 4.5). *Anal.* ($C_9H_{12}FN_3O_5 \cdot 0.5H_2O$) C, H, N, F.

Biological Procedures. The techniques used for assaying the growth inhibitory activity of the analogs in the bacterial and leukemia L-1210 systems and the procedures employed for isolating the fluoropyrimidine resistant strains have been published previously.[7-9]

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Antimalarials. 2.[1] α-Di-*n*-butylaminomethyl-2-(*p*-chlorophenyl)-5-quinazolinemethanol

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The characterization of quinine as a quinolylcarbinolamine led to the synthesis of related compounds, many of which were potent antimalarial agents.[2] The greatest activity was encountered with compounds containing 2-aryl substituents as a deterrent to metabolic inactivation.[3] However, toxic effects due to prolonged photosensitization have, until recently,[4] precluded use of these materials in chemotherapy.[5]

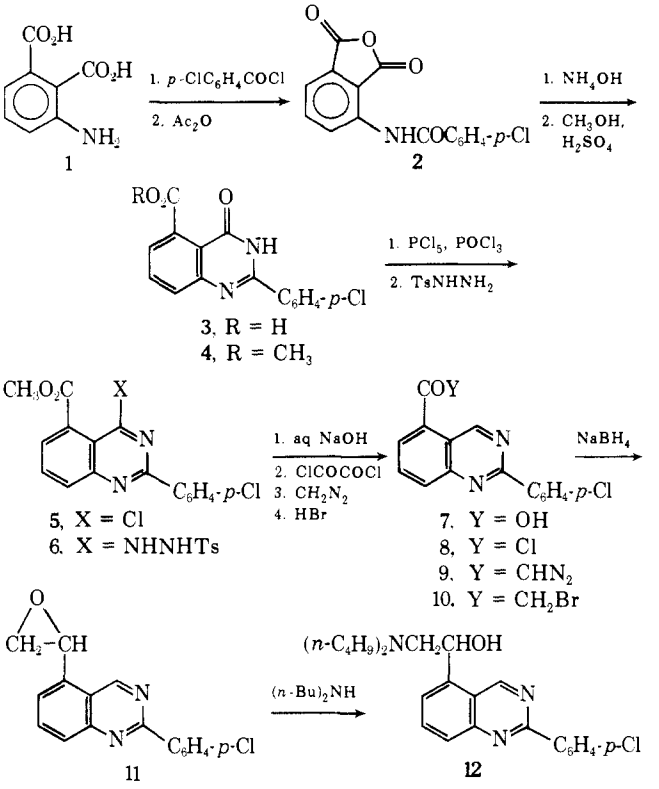
Several quinazoline derivatives are known to possess antimalarial properties.[6] Activity of the natural material Ch'ang Shan, obtained from the roots of *Dichroa febrifuga*, is associated with the alkaloid febrifugine.[7] Synthetic materials include 4-dialkylaminoalkylaminoquinazolines,[8] 2-arylamino-4-dialkylaminoalkylaminoquinazolines,[9] and 2,4-diamino-6-benzylaminoquinazolines.[10]

This report describes the synthesis of a quinazolylcarbinolamine derivative, α-dibutylamino-2-(*p*-chlorophenyl)-5-quinazolinemethanol (**12**). Although it was recognized that incorporation of the 2-aryl substituent could result in toxic photosensitizing effects, the group was included in order to maximize any antimalarial activity.

Chemistry. A modification of a procedure described by Bogert and Jouard[11] for the synthesis of 3,4-dihydro-2-methyl-4-oxo-5-quinazolinecarboxylic acid was used for the preparation 2-(*p*-chlorophenyl)-3,4-dihydro-4-oxo-5-quinazolinecarboxylic acid (**3**). Treatment of 3-aminophthalic acid (**1**) with *p*-chlorobenzoyl chloride gave 3-(*p*-chlorobenzamido)phthalic acid, which was converted to the corresponding anhydride **2** with acetic anhydride. Upon heating with ammonium hydroxide under pressure, **2** was converted directly to **3**. The acid could not be purified but afforded the corresponding methyl ester **4** by acid-catalyzed esterification.

Conversion of the quinazolone **4** to 2-(*p*-chlorophenyl)-5-quinazolinecarboxylic acid (**7**) was effected by the method of Armarego[12] *via* methyl 4-chloro-2-(*p*-chlorophenyl)-5-quinazolinecarboxylate (**5**) and the corresponding 4-(*p*-toluenesulfonylhydrazino) derivative **6**. Elaboration of the carbinolamine side chain closely paralleled methods described for preparation of 2-aryl-4-quinolinemethanol.[13] The acid **7** was converted to the bromomethyl ketone **10** *via* the acid chloride **8** and the diazomethyl ketone **9**. Sodium borohydride reduction afforded 2-(*p*-chlorophenyl)-5-epoxyethylquinazoline (**11**), which upon treatment with di-*n*-butylamine gave the target compound **12** (Scheme I).

Scheme I



Biology. Compound **12** was tested for antimalarial activity against *Plasmodium berghei* in mice[14] and against *P. gallinaceum* in chicks; results are summarized in Table I. Although similar in activity to the 4-quinolinemethanols [*e.g.*, α-(di-*n*-butylaminomethyl)-7-chloro-2-(*p*-chlorophenyl)-4-quinolinemethanol was found to be curative against *P. berghei* in mice at 480 mg/kg], **16** was of no further interest because it also produced the severe photosensitivity observed with the 2-arylquinolinemethanols. Intermediates **4**–**7** were screened and found to be inactive.

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt capillary melting point apparatus and are not corrected. Elemental analyses for those elements indicated by symbols were within ±0.4%. The ir and nmr spectra of all compounds were consistent with the assigned structures.

3-(*p*-Chlorobenzamido)phthalic Acid. A mixture of 3-aminophthalic acid hydrochloride (**1**, 2.18 g, 10 mmol) and $NaHCO_3$ (3.80 g, 45 mmol) in 25 ml of water was treated with *p*-chloro-