reported previously.[16b] 3′-F_3TdR is less than 0.01 as active as F_3TdR in this assay system.

In conclusion, neither compound exhibited sufficient biological activity to warrant further study.

Experimental Section§

1-(3-Deoxy-2,5-di-*O*-*p*-nitrobenzoyl-β-D-*erythro*-pentofuranosyl)-5-trifluoromethyluracil (V). Bis-*O*-(trimethylsilyl)-5-trifluoromethyluracil (I)[6c,9] (3.2 g, 10 mmoles) and 3-deoxy-2,5-di-*O*-*p*-nitrobenzoyl-β-D-*erythro*-pentofuranosyl bromide (III)[10] (4.95 g, 10 mmoles) were stirred under anhydrous conditions with 50 ml of dry acetonitrile at room temperature for 72 hr. The reaction mixture was then treated with MeOH and evaporated under reduced pressure to dryness. The residue was dissolved in $CHCl_3$ and chromatographed on 100 g of Woelm neutral alumina (grade II). The column was eluted with 1 l. of $CHCl_3$ and 1 l. of 15% ethyl acetate in $CHCl_3$ to remove the unreacted sugar. The column was then eluted with 500 ml of MeOH, and all fractions containing V (monitored by tlc on silica gel employing the solvent system 20% ethyl acetate in $CHCl_3$) were combined and evaporated to yield 3.29 g of III (55%): mp 127–130° dec; $\lambda_{max}^{H_2O}$ 264 nm; nmr ($CDCl_3$) τ 3.80 (s, 1, H-1′). *Anal.* ($C_{24}H_{17}N_4O_{11}F_3$) C, H, N.

1-(3-Deoxy-β-D-*erythro*-pentofuranosyl)-5-trifluoromethyluracil (VI). A solution of 3.0 g (5 mmoles) of V and 10 ml of diisopropylamine in 50 ml of dry MeOH was refluxed for 15 min. The reaction mixture was evaporated to dryness and partitioned between water and $CHCl_3$. The organic layers were further extracted with water, and aqueous layers were combined and neutralized with Dowex 50-X4 (H+). The resin was filtered and washed with water and MeOH, and the filtrate was evaporated to a yellowish solid, which was recrystallized from ethanol–ether to give 1.2 g (80%) of VI: colorless crystals; mp 195–196°; $\lambda_{max}^{H_2O}$ 264 nm (ϵ 6300), $\lambda_{max}^{0.1\ N\ HCl}$ 264 nm (ϵ 7500); nmr (D_2O) τ 1.13 (s, 1, H-6), τ 4.20 (s, 1, H-1′); $[\theta]_{268}^{25°}$ +13100. *Anal.* ($C_{10}H_{11}N_2O_5F_3$) C, H, N, F.

Methyl 3-Deoxy-2,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranoside. A solution of 2.2 g (15 mmoles) of methyl 3-deoxy-β-D-*erythro*-pentofuranoside[10] in 50 ml of dry pyridine was cooled in an ice bath and treated with 6.9 g (45 mmoles) of *p*-toluoyl chloride. After stirring at room temperature overnight, the mixture was added with stirring to 100 g of ice and the resulting mixture extracted with ether. The ethereal extracts were combined, washed successively with water, dil H_2SO_4, and satd $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated. The yellowish syrup was purified on 100 g of Woelm neutral alumina (activity grade II) with $CHCl_3$ as the eluant. Evaporation of the solvent yielded 4.1 g (80%) of colorless crystalline methyl 3-deoxy-2,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranoside: mp 80° dec. *Anal.* ($C_{22}H_{24}O_6$) C, H.

3-Deoxy-2,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl Bromide (IV). To an ice-cold solution of 3.8 g (10 mmoles) of methyl 3-deoxy-2,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranoside in 15 ml of glacial AcOH was added 1 ml of acetyl bromide and 15 ml of 42% HBr–AcOH. The solution was kept ice cold for 45 min, whereupon it was evaporated to a viscous oil. Several portions of toluene were successively added and evaporated *in vacuo* to yield IV, 3.46 g (80%), as a faintly colored syrup, which was used without any further characterization.

1-(3-Deoxy-2,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl)-5-fluorouracil and 1-(3-Deoxy-2,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-5-fluorouracil (VII). Bis-*O*-(trimethylsilyl)-5-fluorouracil (II)[13] (2.74 g, 10 mmoles) and IV (3.46 g, 8 mmoles) were stirred in 70 ml of dry acetonitrile for 2 days. Methanol was added and the reaction mixture filtered and evaporated to give a brown glass. This glass was dissolved in $CHCl_3$ and chromatographed on 100 g of silica gel using $CHCl_3$ as eluent. The fractions containing the blocked nucleosides were combined and evaporated to yield 2.56 g (66%) of a colorless glassy solid containing a 6:1 mixture of β and α anomers of VII.

1-(3-Deoxy-β-D-*erythro*-pentofuranosyl)-5-fluorouracil (VIII). The mixture of blocked nucleosides (VII) (2.2 g, 4.5 mmoles) was dissolved in 100 ml of dry MeOH and treated with 1.00 g of NaOMe. The mixture was stirred for 2 hr at room temperature, after which time Dowex 50-X4 (H^+) was added to adjust the pH to 3–4. The resin was filtered and washed several times with MeOH. The filtrate and washings were combined and evaporated to an oil. This oil was extracted repeatedly with ether to remove methyl *p*-toluate, and the resulting solid was chromatographed on 100 g of silica gel with $CHCl_3$ as the eluant. After the residual methyl *p*-toluate was eluted, the column was washed with MeOH to give 850 mg (75%) of the anomeric mixture as a colorless solid. Preparative tlc on 1.75-mm silica gel plates employing a solvent system of ethyl acetate–MeOH–H_2O–heptane, 10:6:5:3 (upper phase),[9] resolved both anomers (R_f β 0.13; α 0.10). After recrystallization from amyl acetate–MeOH, 370 mg (21% based on IV) of VIII was obtained as microcrystals: mp 148° sint, 150–152° dec; $\lambda_{max}^{H_2O}$ 269 nm (ϵ 7210, $\lambda_{max}^{0.1\ N\ NaOH}$ 269 nm (ϵ 6900); nmr (D_2O) τ 1.85 (d, 1, J = 6.0 Hz, H-6), τ 4.15 (s, 1, H-1′), $[\theta]_{270}^{25°}$ + 7700. *Anal.* ($C_9H_{11}N_2O_5F$) C, H, N, F.

§ Melting points were determined on a Thomas-Hoover Apparatus and are uncorrected. Uv spectra were recorded on a Cary spectrophotometer Model 15 and nmr spectra on a Perkin-Elmer Model R12 using tetramethylsilane as internal reference. Circular dichroism spectra were obtained on a Cary spectropolarimeter Model 60. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. All analytical results were within ±0.4% of the theoretical values. Analytical tlc was performed on Eastman Chromatogram Sheets silica gel with fluorescent indicator. Preparative tlc plates were prepared with EM silica gel PF-254 and column chromatography performed with Baker silica gel 60–200 mesh.

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3,5-Disubstituted-6-methyl-2-pyridone. Dihydrazide, Dicarbamate, and Monoaminoalkyl Ester

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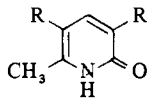
Many pharmacologically active 2-pyridones have been prepared[1] and it was of interest to synthesize simple 2-pyridones bearing known pharmacophores to investigate the efficacy of the 2-pyridone moiety as a carrier and Ph replacement.

In this initial investigation the pharmacophores were the acid hydrazide, $CONHNH_2$, carbamate, $NHCO_2Et$, and 2-dimethylaminoethoxycarbonyl, $CO_2(CH_2)_2NMe_2$ groups, substituted at the 3 and 5 positions of 6-methyl-2-pyridone. All compounds were prepared from 6-methyl-2-pyridone-3,5-dicarboxylic acid[2] (1a). The hydrazide 2 was obtained by treating the corresponding ester[2c,3] 1b with

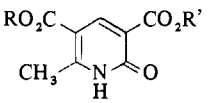


1a, R = CO_2H
1b, R = CO_2Et
2, R = $CONHNH_2$
3, R = $NHCO_2Et$

hydrazine in EtOH. Conversion of the hydrazide to the carbamate was achieved *via* the azide.

Formation of a dimethylaminoethyl ester was not so straightforward. Attempted esterification of the diacid by refluxing a mixture of the acid, 2-dimethylaminoethanol, benzene, and acid catalysts under molecular sieves failed. The disodium salt of the acid did not dissolve in DMF or other common organic solvents and thus frustrated an attempt to condense it with 2-dimethylaminoethyl chloride. Eventually a monodimethylaminoethyl ester was obtained by transesterification when the diethyl ester, dimethylaminoethanol, and benzene were heated in the presence of molecular sieves.

The structure of the mixed ester is postulated as 4 since the mixed ethylmethyl ester 5 gave the same compound when transesterified in a similar manner.



4, R = Et; R' = $(CH_2)_2NMe_2$
5, R = Et; R' = Me

Pharmacological Activity. The compounds were administered ip to groups of 3 mice and the animals observed for changes in motor activity, autonomic features, and reflexes. At high dose levels (200–400 mg/kg) the 3 compounds 2, 3, and 4 produced a degree of sedation, akinesia, and respiratory slowing suggestive of a weak CNS depressant activity. The carbamate 3 caused abdominal contractions at 40 mg/kg.

The compounds were tested for antipentylenetetrazole and antioxotremorine activity by pretreating groups of 6 mice 30 min before challenging with pentylenetetrazole (100 mg/kg ip) or oxotremorine (4 mg/kg ip). No protection was offered.

Antiinflammatory activity was assessed by a rat paw edema test in which the compounds were administered ip 1 hr before injection of a 1% soln of carageenin into the subplantar tissue of the right hind paw. The increase in paw vol was compared with that observed in control animals. The carbamate 3 showed weak activity at 100 mg/kg.

Analgetic activity of the dimethylamino ester 4 was estimated in comparison to a 4% w/v soln of lidocaine in the guinea pig wheal test. An equimolar soln (5%) w/v of the compound had a comparable effect over about one-third of the period of the effect of lidocaine.

In view of the theory[4] that hydrazides exert their toxic effects by interference with vitamin B_6 metabolism the hydrazide 2 was tested for pro- and anti-B_6 activity by its effect upon the growth of *Saccharomyces carlsbergensis*, alone and in competition with B_6. It had no activity in the 5–500 ng/ml range.

Experimental Section

3,5-Dihydrazinocarbonyl-6-methyl-2-pyridone (2). Hydrazine hydrate (100 ml, 2 moles) was added to a soln of 3,5-diethoxycarbonyl-6-methyl-2-pyridone[3] (5 g, 19.8 mmoles) in EtOH (120 ml) and H_2O (100 ml) and the mixt heated to reflux for 24 hr. The ppt (3.05 g) was removed by filtration. More material (1.16 g) was obtd by evapg the filtrate and H_2O washing the solid to remove hydrazine. Crystn from H_2O gave the dihydrazide: mp 344–347° dec; ir (KCl, cm^{-1}) 1670, 1615. *Anal.* C, H, N.

Another run as above but worked up after only 90-min heating gave material from which a substance believed to be the monohydrazide (3-$CONHNH_2$ in analogy with the transesterification product) was isolated in 6% yield, as a $CHCl_3$-soluble component, in addn to the dihydrazide ($CHCl_3$-insoluble): mp 260° dec; ir (KCl, cm^{-1}) 1715, 1705, 1695, 1685.

3,5-Bisethoxycarbonylamino-6-methyl-2-pyridone (3). $NaNO_2$ (2.76 g, 40 mmoles) in H_2O (50 ml) was added dropwise to a vigorously stirred soln of the dihydrazide 2 (4.13 g, 19.3 mmoles) in 10% aqueous HCl (36 ml, 100 mequiv) maintained at 0°. The suspension which soon formed was stirred for 1 hr at 0°. Filtration afforded the crude diazide: ir (KCl, cm^{-1}) 2120, 1680.

The diazide (3.7 g, 15 mmoles) in abs EtOH (250 ml) was heated to reflux for 2.5 hr. Concn of the soln and cooling afforded the carbamate, 53% from hydrazide: mp 237–238° (EtOH); ir (KCl, cm^{-1}) 1730, 1685, 1660, 1633. *Anal.* C, H, N.

3-(2-Dimethylaminoethoxycarbonyl)-5-ethoxycarbonyl-6-methyl-2-pyridone (4). A. From the Diethyl Ester. 3,5-Diethoxycarbonyl-6-methyl-2-pyridone[3] (5 g, 19.7 mmoles), 2-dimethylaminoethanol (100 ml, *ca.* 1 mole), and dry PhH (200 ml) were heated to reflux beneath a Soxhlet contg 4A molecular sieves (40 g) for 132 hr. The progress of reaction was monitored by tlc. The mixt was concd to small vol when the addn of Et_2O (100 ml) caused pptn of a brown semicryst solid. Crystn from PhH gave white needles (3.5 g, 60%): mp 172–173°; ir (KCl, cm^{-1}) 1715, 1695, 1665; nmr ($CDCl_3$, τ) −0.15 (bd, 1), 1.21 (s, 1), 5.4–5.88 (q + t, 4), 7.13–7.4 (s + t, 5), 7.66 (s, 6), 8.63 (t, 3). *Anal.* C, H, N.

B. From the 5-Ethyl-3-methyl Diester. 5-Ethoxycarbonyl-3-methoxycarbonyl-6-methyl-2-pyridone (500 mg, 21 mmoles), dimethylaminoethanol (10 ml), dry PhH (20 ml), and 4A molecular sieves (4 g) were refluxed for 12 hr to achieve partial reaction. Chromatog on silica gel of the product obtained as in A gave an essentially pure fraction whose nmr spectrum was identical with that of the product from A.

5-Ethoxycarbonyl-3-methoxycarbonyl-6-methyl-2-pyridone (5). Benzylamine and 3,5-diethoxycarbonyl-6-methyl-2-pyrone[2b] were allowed to react in EtOH and the product washed with dil HCl to yield *N*-benzyl-5-ethoxycarbonyl-6-methyl-2-pyridone-3-carboxylic acid: mp 135–136°; esterification with CH_2N_2 gave the 3-Me ester, a gum, hydrogenolyzed over Pd/C in EtOH to give the required compound: mp 194–196° (MeOH–PhH–petr ether); ir (KCl, cm^{-1}) 1710, 1665, nmr ($CDCl_3$, τ) −3.1 (bd, 1), 1.0 (s, 1), 5.6 (q, J = 7 cps, 2), 6.0 (s, 3), 7.11 (s, 3), 8.56 (t, 3).

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