

Ronald A. Henry (1) and Peter R. Hammond (2)

Code 385, Chemistry Division, Naval Weapons Center, China Lake, California 93555

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7-Amino- and 7-hydroxy-1,4-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridines, as well as the homologous 1,2,4-trimethyl derivatives, have been synthesized. Condensation of these compounds with β -keto esters gave substituted tetrahydro-1,2-dihydropyrido- or 2*H*-pyrano-[2,3-*b*]-[1,8]naphthyridines, which are stable fluorescers (range 393-482 nm in ethanol) and laser dyes. Several related compounds are described.

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As part of a program on the preparation and evaluation of fluorescent materials as dyes for lasers (3-7), several new 2-amino- and 2-hydroxy-1,8-naphthyridine compounds have been made and then condensed with various β -keto esters, using established methods, to yield derivatives of pyrido- and pyranonaphthyridines. The reaction sequences are shown in Figure 1; procedures for the synthesis of both the precursors and the dyes are found in the Experimental. Table I summarizes pertinent information about the preparation and properties of the 1,2-dihydropyrido- and 2*H*-pyrano[2,3-*b*][1,8]naphthyridines. Although ^1H nmr spectra were obtained on all new compounds in order to confirm the structure assignments, data have been included with the experimental details for only representative examples.

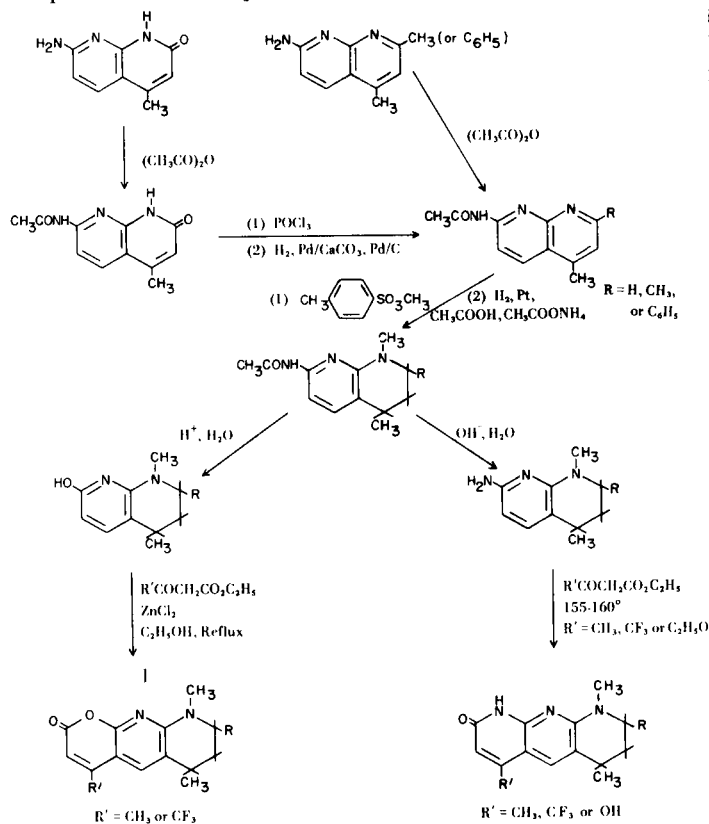
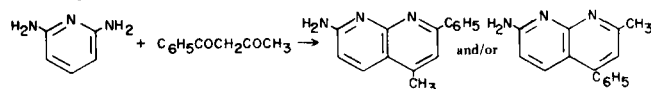


Figure 1. Reaction steps to substituted-6,7,8,9-tetrahydropyrido- and 2*H*-pyrano[2,3-*b*]naphthyridines

Several features about the reactions involved should be mentioned briefly. The quaternarization of the 7-acetamido-4-methyl- or 2,4-disubstituted-1,8-naphthyridines with methyl *p*-toluenesulfonate, ethyl bromoacetate or benzyl chloride occurred primarily, if not exclusively, on the nitrogen of the pyrido ring with the alkyl substituents. The same ring was also reduced when these quaternary salts were hydrogenated; the C-methyl groups appeared as doublets (splitting by a methine proton) in the ^1H nmr spectra. However, when unquaternarized 7-acetamido-2,4-dimethyl-1,8-naphthyridine was hydrogenated under the same conditions, the pyrido ring with the acetamido group was reduced to the tetrahydro derivative. In this case, the C-methyl groups appeared as singlets in the ^1H nmr spectrum. Partial hydrogenolysis of the acetamido group also was noted. The mode of hydrolysis of the 7-acetamido-substituted-1,2,3,4-tetrahydro-1,8-naphthyridines was significantly different under acidic and basic conditions, the former giving 7-hydroxy derivatives, the latter 7-amino. Thus, convenient entry into two series of compounds was possible from the same precursor.

The condensation of benzoylacetone with 2,6-diamino- could give two isomers:

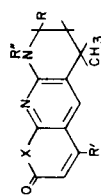


The former structure was assigned to the product isolated in low yield on the basis of the ^1H nmr of its *N*-methyl-tetrahydro derivative. The downfield methine (CH adjacent to N) was always a doubled doublet resulting from



the splitting of the methine proton by the $\text{H}_{\text{axial}}\text{-H}_{\text{equatorial}}$ protons on the adjacent methylene group. If the methyl rather than the phenyl group had been in this position, this doubled doublet would have been further split by the methyl protons to give a complex multiplet. The stereochemistry of the various tetrahydro compounds was not determined.

Table I
Substituted 1,2-Dihydropyrido- and 2H-Pyran[2,3-b][1,8]naphthyridines



X	R'	R	R''	Empirical formula	Yield (a) %	M.p., °C	Recrystallization solvent	Fluorescence max. in ethanol (Excited, nm)	Analysis			
									C, % (Theory)	H, % (Theory)	N, % (Theory)	F, % (Theory)
O	H(b)	CH ₃	CH ₃	C ₁₄ H ₁₆ N ₂ O ₂	30	111-112	1:1 C ₆ H ₆ -C ₆ H ₁₂	437 (375)	69.06 (68.82)	6.57 (6.60)	11.08 (11.47)	...
O	CH ₃	CH ₃	CH ₃	C ₁₅ H ₁₈ N ₂ O ₂	11	189-190	50% ethanol	430 (375)	69.95 (69.74)	6.39 (7.02)	10.79 (10.80)	...
O	CF ₃	H	CH ₃	C ₁₄ H ₁₃ F ₃ N ₂ O ₂	95	163.5-154.5	65% ethanol	482 (400)	56.2 (56.37)	4.33 (4.39)	9.36 (9.39)	19.35 (19.11)
O	CF ₃	CH ₃	H	C ₁₄ H ₁₂ F ₃ N ₂ O ₂	...	210-212	95% ethanol	473 (395)	56.05 (56.37)	4.51 (4.39)	9.22 (9.39)	...
O	CF ₃	CH ₃	CH ₃	C ₁₅ H ₁₅ F ₃ N ₂ O ₂	91	167-168	75% ethanol	480 (394)	57.91 (57.69)	5.00 (4.84)	8.77 (8.97)	18.54 (18.25)
O	CF ₃	CH ₃	CH ₂ CO ₂ C ₂ H ₅	C ₁₈ H ₁₉ F ₃ N ₂ O ₄	55	136-138	Cyclohexane	474 (390)	56.35 (56.25)	4.89 (4.98)	7.19 (7.29)	15.00 (14.83)
O	CF ₃	C ₆ H ₅	CH ₃	C ₂₀ H ₁₇ F ₃ N ₂ O ₄	23	146.5-147.5	Cyclohexane	479 (395)	64.42 (64.16)	4.72 (4.58)	7.34 (7.48)	15.40 (15.23)
NH	CH ₃	H	CH ₃	C ₁₄ H ₁₇ N ₃ O (d)	29	254-256	C ₆ H ₆	409 (375)	69.26 (69.11)	6.93 (7.04)	17.32 (17.27)	...
NH	CH ₃	CH ₃	CH ₃	C ₁₅ H ₁₉ N ₃ O	26	245-246	C ₆ H ₆	408 (370)	69.96 (70.01)	7.40 (7.44)	16.28 (16.33)	...
NH	CF ₃	H	CH ₃	C ₁₄ H ₁₄ F ₃ N ₃ O	86	232.5-233.5	C ₆ H ₆	440 (390)	56.55 (56.56)	4.68 (4.75)	14.05 (14.14)	18.77 (19.17)
NH	CF ₃	CH ₃	CH ₃	C ₁₅ H ₁₆ F ₃ N ₃ O	90	246-248	C ₆ H ₆	442 (390)	57.40 (57.87)	5.14 (5.18)	13.17 (13.50)	...
NH	OH(e)	H	CH ₃	C ₁₃ H ₁₅ N ₃ O ₂	85	> 300	30% ethanol	...	63.58 (63.66)	6.06 (6.16)	16.92 (17.13)	...
NH	OCH ₃ (f)	H	CH ₃	C ₁₄ H ₁₇ N ₃ O ₂	49	246-247	Acetone	393 (360)	64.39 (64.84)	6.57 (6.61)	15.96 (16.21)	...

(a) For the reaction of the hydroxy or aminotetrahydronaphthyridine with the appropriate β -keto ester. (b) Made from 2 and malic acid in concentrated sulfuric acid at 120° for 1 hour. (c) Recovered in low yield as a by-product in the preparation of the compound where R'' = CH₂CO₂C₂H₅. (d) The picrate after recrystallization from ethanol melted 213-214°. Found: N, 17.77; theory, 17.79. (e) Equivalent amounts of diethyl malonate and 1 were heated with stirring in diphenyl ether at 170-180° for 1 hour; then the temperature was slowly raised during 2.5 hours to 245°. The product, which separated in part from the hot solution, was recovered by diluting the cooled mixture with benzene, chilling, filtering, and washing, first with cold benzene, then with hexane. Based on both the ir and the ¹H nmr the compound exists mainly in the 3-methylene-4 keto form. (f) Made by methylating the previous compound with dimethyl sulfate at 55-60° in basic 33% ethanol.

The effect of kind and position of substituents on the fluorescence maximum is the same as that observed (6) with other coumarin and quinolone dyes. The most pronounced influence on the chromophore is noted with changes in the substituents on the carbonyl-containing ring. When R' is the electron-withdrawing trifluoromethyl group (see formula, Table I), the fluorescence is red-shifted approximately 50 nm with the azacoumarins and 30-35 nm with the azaquinolones compared to the corresponding compounds with R' = CH₃. An electron-donating group, such as methoxyl, causes a 15-20 nm blue-shift in the fluorescent maximum compared to the analogous methyl compound; even a methyl group produces a small blue-shift when compared with the compound in which R' = H. Changes in R and R'' influence only slightly the position of the fluorescence maximum. The fluorescence of the azaquinolone dyes is always blue-shifted 20-40 nm over that of the corresponding azacoumarins.

Two of the compounds described here, 2-oxo-6,9-dimethyl- and 2-oxo-6,7,9-trimethyl-4-trifluoromethyl-6,7,8,9-tetrahydro-2H-pyran[2,3-b][1,8]naphthyridine (Laser Dyes AC2F and AC3F, respectively), show a relatively high stability (reduced photochemical degradation) toward repeated flash lamp pumping (5,8).

EXPERIMENTAL

7-Acetamido-2-chloro-4-methyl-1,8-naphthyridine.

This compound was made from 7-acetamido-2-hydroxy-4-methyl-1,8-naphthyridine by the procedure of Petrow, Rewald, and Sturgeon (9). The latter compound is also described by the same authors.

7-Acetamido-4-methyl-1,8-naphthyridine.

The above chloro compound (11.8 g., 0.05 mole) was slurried with 200 ml. of 3% potassium hydroxide in 95% ethanol, 2 g. of 5% palladium/calcium carbonate and 10-20 mg. of 10% palladium/carbon, and hydrogenated at 50 psi. After an induction period the pressure rapidly dropped 3.5-3.6 lb. The solution was filtered through Celite to remove the catalyst and the cake washed well with ethanol. The filtrate and washings were evaporated to dryness. The residue was slurried with 25 ml. of cold water, and the solid filtered, washed with two 10-ml. portions of water and dried; 5.8 g. (73%), m.p. 201-204°, of 7-amino-4-methyl-1,8-naphthyridine. Ether extraction of the mother liquors plus washings yielded 0.62 g. (8%) more.

Recrystallization of 2.5 g. from 130 ml. of 9:1 benzene-ethanol gave a mixture of golden needles and white crusts, both of which melted at 204.5-205.5° and both of which had the same ¹H nmr spectra. The ir spectrum of the golden needles suggested a hydrated form of 7-amino-4-methyl-1,8-naphthyridine (confirmed by analysis).

Anal. Calcd. for C₉H₉N₃·0.5H₂O: C, 64.27; H, 5.99; N, 24.98. Found: C, 64.26; H, 5.97; N, 24.84.

Anal. on white crusts. Calcd. for C₉H₉N₃: C, 67.90; H, 5.70; N, 26.40; mol. wt. 159. Found: C, 67.94; H, 5.63; N, 26.43; mol. wt. (mass spec.) 159.

The free 7-amino compound (12.0 g.) was reconverted to the 7-acetamido by refluxing with 30 ml. of acetic anhydride for 1

hour. The cooled solution was slurried with 100 g. of ice plus 100 ml. of cold water, neutralized with sodium bicarbonate, warmed to dissolve all solids, then cooled overnight at 5°. The crystalline product was filtered, washed twice with cold water and dried; 13.3 g. (88%); m.p. 248-251° dec. An additional 2.2 g. (m.p. 240-250°) could be recovered by saturating the remaining aqueous phase with sodium chloride. When recrystallized from acetonitrile, the compound melted at 252-253° dec.

Anal. Calcd. for C₁₁H₁₁N₃O: C, 65.65; H, 5.51; N, 20.88. Found: C, 65.49; H, 5.51; N, 20.72.

A small quantity of a diacetylated product, m.p. 145.5-146.5°, after recrystallization from benzene-*n*-hexane, was isolated from one experiment.

Anal. Calcd. for C₁₃H₁₃N₃O₂: C, 64.18; H, 5.39; N, 17.27. Found: C, 64.16; H, 5.45; N, 17.32.

7-Acetamido-1,4-dimethyl-1,8-naphthyridinium *p*-Toluenesulfonate.

7-Acetamido-4-methyl-1,8-naphthyridine (13.3 g., 0.066 mole) was refluxed for 8 hours with 12.7 g. of methyl *p*-toluenesulfonate in 150 ml. of dry acetonitrile. The dark purple solution was cooled at 5° for several days; 21.8 g. (85%) of felted needles, m.p. 200-202°, was removed. Addition of a large volume of ether to the mother liquors precipitated 2.3 g. (9%) more of the salt; m.p. 185-190°. The ¹H nmr was consistent with that expected for the desired product.

7-Acetamido-1,4-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine.

The previous salt (11.6 g., 0.03 mole) was hydrogenated over 0.15 g. of platinum oxide in 100 ml. of glacial acetic acid containing 12 g. of ammonium acetate. Hydrogen uptake essentially ceased after the pressure dropped from 50 to 45 psi after 4 hours; the purple solution became colorless. The catalyst was removed, washed once with 20 ml. of acetic acid and twice with 20 ml. of water. The combined solutions were reduced to dryness on a rotary evaporator. The residual was dissolved in 100 ml. of water, cooled to 5°, made basic and ether extracted (2-100 ml.); the latter extracts, after washing once with a small volume of water, were dried over potassium carbonate. Evaporation left 5.34 g. (81%) of off-white solid, melting sharply at 95-96°; ¹H nmr (60 MHz, deuteriochloroform): δ 1.20 (d, 3H, CH₃CH-, J = 7 Hz), 1.5-2.0 (m, 2H, H₃, H₃), 2.04 (s, 3H, CH₃CO), 2.6-3.0 (m, 1H, CH₃CH-), 3.03 (s, 3H, N-CH₃), 3.32 (t, 2H, H₂, H₂, J = 6 Hz), 7.22 (broad s, 2H, H₅, H₆), 8.08 (broad s, 1H, -NH-).

7-Amino-1,4-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (1).

7-Acetamido-1,4-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (3.6 g.) in 50 ml. of 5% potassium hydroxide in 95% ethanol was refluxed for 8 hours under nitrogen. The solvent was then removed on a rotary evaporator and the residue slurried with 30 ml. of water. After cooling to 5° the solid product was removed, washed three times with cold water and dried, 2.82 g. (97%), m.p. 51-53°. The amide carbonyl absorption had disappeared completely from the ir spectrum, which was also different from that for the 7-hydroxy compound obtained by acid hydrolysis of the amide. Recrystallization from *n*-hexane (0.5 g./10 ml.) by cooling to -15° furnished coarse, white grains, m.p. 52.5-53.5°; ¹H nmr (deuteriochloroform): δ 1.17 (d, 3H, -CH-CH₃, J = 7 Hz), 1.69 (m, 2H, H₃, H₃), 2.72 (m, 1H, H₄), 3.05 (s, 3H, NCH₃), 3.27 (t, 2H, H₂, H₂), 4.10 (broad s, 2H, NH₂), 5.72 (d, 1H, H₆, J = 8 Hz), 7.02 (d, 1H, H₅, J = 8 Hz); fl. max (ethanol): 373 nm (exc. 325 nm); fl. max (10⁻³ N perchloric acid in ethanol): 416 nm (exc. 350 nm).

Anal. Calcd. for C₁₀H₁₅N₃: C, 67.76; H, 8.53; N, 23.71.

Found: C, 68.19; H, 8.38; N, 23.36.

7-Hydroxy-1,4-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine.

7-Acetamido-1,4-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (1.27 g.) was dissolved in 16 ml. of 6*N* hydrochloric acid, allowed to stand 3 days at 25°, then heated in the steam bath for 5 hours. The solution was cooled in an ice bath, made basic and the oily product which separated extracted into ether (some ether insoluble solid was removed by filtration). Evaporation of the dried ethereal solution left 0.38 g. (37%) of a solid melting at 134-136°. Golden plates, m.p. 134-135°, were obtained by recrystallization from cyclohexane. The ¹H nmr spectrum is consistent with the assigned structure.

Anal. Calcd. for C₁₀H₁₄N₂O: C, 67.38; H, 7.92; N, 15.72; mol. wt. 178.2. Found: C, 67.36; H, 8.02; N, 15.61; mol. wt. (mass spec.) 178.

7-Amino-2,4-dimethyl-1,8-naphthyridine.

2,6-Diaminopyridine (43.6 g., 0.4 mole), 40.0 g. (0.4 mole) of 2,4-pentanedione, 200 ml. of glacial acetic acid and 5 ml. of 96% sulfuric acid were mixed, then refluxed with stirring for 24 hours. The cold solution was added slowly with good stirring and ice bath cooling to 160 g. of sodium hydroxide in enough water to make 600 ml. The brown solid, which crystallized, was filtered after the solution had been cooled overnight at 5°, washed twice with cold water and dried, 25.3 g., m.p. 125-200°. This crude material was dissolved in 130 ml. of boiling 95% ethanol and the solution chilled overnight at -15°, 19.5 g. (28%), m.p. 215-220°. This material was suitable for the following experiment. Ochiai and Miyaki (10) reported m.p. 220°; they performed the condensation at 120-130° with anhydrous zinc chloride and no solvent.

7-Acetamido-1,2,4-trimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine.

This compound was made in 72% yield from the previous material using the same sequence of reactions described above for the corresponding dimethyl derivative: acetylation, methylation, and hydrogenation. The white, felted needles after recrystallization from cyclohexane melted 152.5-153.5°.

Anal. Calcd. for C₁₃H₁₉N₃O: C, 66.92; H, 8.21; N, 18.01. Found: C, 67.03; H, 8.52; N, 17.84.

7-Hydroxy-1,2,4-trimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (2).

The previous compound (3.2 g.) was heated for 18 hours on the steam bath with 40 ml. of 6*N* hydrochloric acid. The cooled solution was neutralized with 25% aqueous sodium hydroxide; the orange oil which separated soon crystallized. It was removed, washed with water and dried; 2.66 g. (100%), m.p. 143-145°. Recrystallization from 8:2 cyclohexane-benzene, with carbon decolorization, gave white grains, m.p. 146-148°.

Anal. Calcd. for C₁₁H₁₆N₂O: C, 68.71; H, 8.39; N, 14.57. Found: C, 68.20; H, 8.67; N, 14.52.

7-Amino-1,2,4-trimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine.

The viscous oil recovered from the alkaline hydrolysis of the corresponding 7-acetamido compound was used without further purification.

2-Oxo-6,9-dimethyl-4-trifluoromethyl-6,7,8,9-tetrahydro-2H-pyrano[2,3-*b*][1,8]naphthyridine.

The following procedure is typical of that used to prepare the various azacoumarins. 7-Hydroxy-1,4-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (0.19 g.), 1.2 ml. of ethyl trifluoroacetate, 50 mg. of anhydrous zinc chloride, and 10 ml. of absolute ethanol

were refluxed for 40 hours. The cooled solution was poured with stirring into 50 ml. of water plus 3 ml. of hydrochloric acid; the yellow precipitate was filtered, washed with water, and dried (0.31 g., 95%). Solvent used for recrystallization, melting point, fluorescence data and analytical data are summarized in Table I. The ¹H nmr spectral data (deuteriochloroform, 100 MHz) on the analogous 6,8,9-trimethyl derivative are: δ 1.37 (d, 6H, CH₃CH), 1.47 (m, 1H, H_{7b}), 2.10 (dt, 1H, H_{7a}, J = 13 Hz, J = 4 Hz), 2.80 (m, 1H, H₆), 3.20 (s, 3H, NCH₃), 3.70 (m, 1H, H₈), 6.38 (s, 1H, H₃), 7.41 (q, 1H, H₅, J_{H₅-CF₃} = ~1.5 Hz).

2-Oxo-6,9-dimethyl-4-trifluoromethyl-1,2,6,7,8,9-hexahydro-pyrano[2,3-*b*][1,8]naphthyridine.

This is a representative procedure for making azaquinolones. 7-Amino-1,4-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine (0.9 g.) and 1.0 g. of ethyl trifluoroacetate were heated at 145-165° for 18 hours. The cooled, semisolid mass was slurried with 5 ml. of ether, filtered and washed with more ether, 1.3 g., m.p. 225-230°, wet 200°. Other data are found in Table I; ¹H nmr (deuteriochloroform, 100 MHz): δ 1.30 (d, 3H, CH₃CH, J = 7 Hz), 1.74 (m, 1H, H_{7a} or H_{7b}), 1.89 (m, H, H_{7a} or H_{7b}), 2.92 (m, 1H, H₆), 3.20 (s, 3H, NCH₃), 3.49 (t, 2H, H₈, H₈, J = 6 Hz), 6.62 (s, 1H, H₃), 7.46 (q, 1H, H₅, J_{H₅-CF₃} = ~1.5 Hz), 9.40 (broad s, 1H, NH).

7-Amino-4-methyl-2-phenyl-1,8-naphthyridine.

2,6-Diaminopyridine (16.4 g., 0.15 mole), 24 g. of benzoyl-acetone, 75 ml. of acetic acid and 1.5 ml. of 96% sulfuric acid was refluxed with stirring for 24 hours. The solution was poured slowly with stirring into 50 g. of sodium hydroxide in 250 ml. of water; the temperature was held 20-30° by cooling. The tan solid was filtered, washed well with water and dried, 21.8 g. One recrystallization from 100 ml. of 95% ethanol gave 6.9 g. of coarse needles, m.p. 65-190°; a second recrystallization from 50 ml. of ethanol furnished 2.1 g. (6%) of the title compound, m.p. 253-255°; ¹H nmr (deuteriochloroform + DMSO-d₆, 60 MHz): δ 2.67 (s, 3H, CH₃), 6.20 (broad exchangeable s, 2H, NH₂), 6.92 (d, 1H, H₅, J = 9 Hz), 7.58 (d, 1H, H₆), 7.50 (m, 3H, *meta* and *para* protons on C₆H₅), 8.30 (m, 2H, *ortho* protons on C₆H₅).

Anal. Calcd. for C₁₅H₁₃N₃: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.99; H, 5.62; N, 17.96.

From the aqueous mother liquors from which the above compound had been isolated there was recovered upon cooling 6.3 g. of an off-white solid. Recrystallization from water gave felted, white needles, melting in part 190-192°, the balance 205-207°. The ¹H nmr suggested a mixture of tautomeric and/or isomeric diacetyldiaminopyridines.

Anal. Calcd. for C₉H₁₁N₃O₂: N, 21.76. Found: N, 21.54.

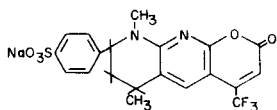
2-Oxo-6,9-dimethyl-8-phenyl-4-trifluoromethyl-6,7,8,9-tetrahydro-2H-pyrano[2,3-*b*][1,8]naphthyridine.

7-Amino-4-methyl-2-phenyl-1,8-naphthyridine (2.0 g.) was mixed with 4 ml. of acetic anhydride; the solution was allowed to stand 1 hour at 25°, refluxed for 3 hours, cooled, and diluted with 15 ml. of water. After the excess anhydride hydrolyzed, the solution was made slightly basic with 25% aqueous sodium hydroxide (cooling used). The precipitated solid was filtered, washed well with cold water and dried, 2.3 g. (98%), m.p. 209.5-210.5° after partial melting and resolidification at 150-160°.

All of the above amide was refluxed for 8 hours in 25 ml. of dry acetonitrile with 1.6 g. of methyl *p*-toluenesulfonate. Cooling and addition of a large excess of ether yielded 3.34 g. (88.5%) of a blue-purple solid. The salt in 25 ml. of acetic acid containing 3 g. of ammonium acetate was hydrogenated over 0.1 g. of platinum

oxide at an initial pressure of 50 psi; the theoretical amount (2 mole equivalents) was rapidly absorbed. The catalyst was removed, washed with 3 ml. of acetic acid, and two 10-ml. portions of water; the combined filtrates were evaporated to thick syrup which was then dissolved in 75 ml. of 65% ethanol and made basic with 25% aqueous sodium hydroxide. Water (75 ml.) was added to precipitate the product which was filtered off after overnight cooling at 5°. After washing with cold water, the wet, crude 7-acetamido-1,4-dimethyl-2-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine was heated overnight on the steam bath with 30 ml. of 6*N* hydrochloric acid. Cooling, followed by careful neutralization with sodium hydroxide solution, furnished 1.2 g. of the 7-hydroxy derivative. The latter (a pale orange powder) melted at 211-213° after one recrystallization from 60 ml. of 95:5 benzene-ethanol; ¹H nmr (deuteriochloroform, 60 MHz): δ 1.30 (d, 3H, CH₃CH, J = 6.5 Hz), 1.6-2.6 (m, 3H, H₃, H₃, H₄), 3.10 (s, 3H, NCH₃), 4.72 (dd, 1H, H₂, J = 4 Hz, J = 10 Hz), 6.19 (d, 1H, H₅, J = 9.5 Hz), 7.43 (s, 5H, C₆H₅), 7.60 (d, 1H, H₆, J = 9.5 Hz), 12.1 (broad s, 1H, OH, or NH).

A solution consisting of 0.7 g. of the 7-hydroxy-1,4-dimethyl-2-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine, 3 ml. of ethyl trifluoroacetate, 20 ml. of absolute ethanol and 0.47 g. of anhydrous zinc chloride was refluxed for 64 hours. After cooling, the solution was diluted with 20 ml. of water plus 1 ml. of concentrated hydrochloric acid. The yellow solid which precipitated was filtered, washed with water and dried, 0.24 g. (23%). Other data can be found in Table I. The position of the phenyl group in this compound was assigned on the basis of the analysis of the ¹H nmr spectrum of its precursor and of the following sulfonated derivative.



The previous compound was sulfonated with 20% oleum (15-20°, 4 hours). After quenching on ice, neutralizing with sodium bicarbonate and evaporating the solution to dryness, the sulfonate was extracted with boiling 95% ethanol. The product crystallized from the cooled extracts upon the addition of diethyl ether (40 ethanol - 30 ether); fl. max (water): 473 nm (exc. 390 nm). The phenyl group was assigned to the 8-position rather than the 6-position based on the following ¹H nmr evidence: the downfield methine proton again appeared as a quartet (splitting by the H₇ axial and H₇ equatorial protons) rather than a very complex multiplet one would expect if a methyl group were in the 8-position.

Anal. Calcd. for C₂₀H₁₆F₃N₂O₅SNa·2.5H₂O: F, 10.93; N, 5.37; S, 6.15. Found: F, 10.96; N, 5.27; S, 6.18.

7-Acetamido-2,4-dimethyl-5,6,7,8-tetrahydro-1,8-naphthyridine and 2,4-Dimethyl-5,6,7,8-tetrahydro-1,8-naphthyridine.

7-Acetamido-2,4-dimethyl-1,8-naphthyridine (5.6 g.) was hydrogenated over platinum oxide (0.12 g.) in acetic acid (70 ml.) containing ammonium acetate (10 g.); about 5 hours were required to absorb the theoretical amount of hydrogen. The basic product recovered in the usual manner was a gum; extraction with boiling benzene left a poorly soluble white solid, wetting at 190° and melting 197-198°. Cooling the benzene extracts yielded white crystals also melting 193-197°. The ¹H nmr on this solid indicated reduction of the pyrido ring possessing the acetamido group rather than the one with the methyl groups; the methyl signals were sharp singlets, rather than the doublets (J = 6-7 Hz) normally seen when the methyl containing ring was reduced.

Anal. Calcd. for C₁₂H₁₇N₃O: C, 65.72; H, 7.82; N, 19.16; mol. wt., 219.28. Found: C, 65.90; H, 7.88; N, 19.04, 19.14; mol. wt. (mass spec.), 219.

What appears to be another epimer was isolated in low yield from another experiment; flat needles, m.p. 155-160° after recrystallization of 1:1 benzene-cyclohexane. The ir spectrum was different than that for the above compound. Its picrate melted 163-164° after recrystallization from ethanol.

Anal. Calcd. for C₁₈H₂₀N₆O₈: C, 48.21; H, 4.50; N, 18.75. Found: C, 48.14; H, 4.82; N, 18.58.

Evaporation of the benzene mother liquors left a low melting solid which was recrystallized several times from *N*-hexane; flat needles, m.p. 115-116°. No amide carbonyl was present in the ir spectrum. The ¹H nmr indicated that this compound was 2,4-dimethyl-5,6,7,8-tetrahydro-1,8-naphthyridine, which resulted from the hydrogenolysis of the acetamido group. ¹H nmr (deuteriochloroform, 100 MHz): δ 1.8-2.2 (multiplet, 2H, H₆, H₆); 2.10 (s, 3H, 4-CH₃), 2.27 (s, 3H, 2-CH₃), 2.70 (t, 2H, H₅, H₅, J = 6 Hz), 3.35 (sextet, 2H, H₇, H₇, J_{H₆H₇} = 6 Hz, J_{NH-H₇} = 2.5 Hz, collapses to a triplet when exchanged with deuterium oxide), 4.72 (broad, exchangeable peak, 1H, NH), 6.28 (s, 1H, H₃).

Anal. Calcd. for C₁₀H₁₄N₂: mol. wt., 162.23. Found: Mol. (mass spec.), 162.

7-Acetamido-1-carboethoxymethylene-2,4-dimethyl-1,2,3,4-tetrahydro-1,8-naphthyridine.

The reaction product (9.4 g.) of ethyl bromoacetate and 7-acetamido-2,4-dimethyl-1,8-naphthyridine was hydrogenated by the same procedure used for the analogous methyl compounds. Work-up in a similar manner gave 5.3 g. (71%) of crude product, m.p. 100-104°. One recrystallization from *n*-hexane gave pale yellow blades, m.p. 110-111°.

Anal. Calcd. for C₁₆H₂₃N₃O₃: C, 62.93; H, 7.59; N, 13.76. Found: C, 62.94; H, 7.57; N, 13.69.

The crude 7-hydroxy compound obtained by acid hydrolysis was used for the preparation of the azacoumarin without purification.

7-Acetamido-2,4-dimethyl-1,8-naphthyridine Hydrobromide.

After recrystallization from acetonitrile this salt decomposed 252-254°.

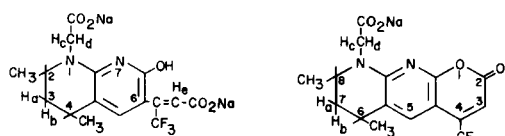
Anal. Calcd. for C₁₂H₁₄BrN₃O·H₂O: Br, 25.43; N, 13.37. Found: Br, 25.59; N, 13.29.

7-Acetamido-1-benzyl-2,4-dimethyl-1,8-naphthyridine Chloride.

7-Acetamido-2,4-dimethyl-1,8-naphthyridine (6.45 g.), 4 g. of benzyl chloride and 80 ml. of dry acetonitrile were refluxed for 88.5 hours. Complete solution was never attained. After cooling to 5° the solid was removed and washed with four 50 ml. portions of ether; 5.3 g. (82%) of starting amide. Cooling the combined filtrate and ether washings yielded 1.2 g. (11%) of the title compound. Recrystallization from ethanol-ether gave dark green crystals, m.p. 185-190° dec.; ¹H nmr (DMSO-d₆, 60 MHz): δ 2.23 (s, 3H, CH₃CO), 2.92 (s, 6H, CH₃C), 6.49 (s, 2H, CH₂), 7.39 (s, 5H, C₆H₅), 8.10 (s, 1H, H₃), 8.64 (d, 1H, H₅, J = 9 Hz), 9.08 (d, 1H, H₆, J = 9 Hz), 11.90 (s, 1H, NH).

Anal. Calcd. for C₁₉H₂₀ClN₃O·1.5H₂O: Cl, 9.61; N, 11.39. Found: Cl, 9.75; N, 11.46.

Disodium 3-(6-[2,4-Dimethyl-1-carboxymethylene-7-hydroxy-1,2,3,4-tetrahydro-1,8-naphthyridyl]) 4,4,4-Trifluorocrotonate and Sodium 2-Oxo-6,8-dimethyl-9-carboxymethylene-4-trifluoromethyl-6,7,8,9-tetrahydro-2*H*-pyrano[2,3-*b*][1,8]naphthyridine.



2-Oxo-6,8-dimethyl-9-carboethoxymethylene-4-trifluoromethyl-6,7,8,9-tetrahydro-2H-pyrano[2,3-b][1,8]naphthyridine (0.5 g.) was dissolved in a solution consisting of 0.9 g. of sodium hydroxide in 10 ml. of 50% ethanol and allowed to stand overnight at 2°. The solution was diluted with 5 ml. of ethanol, made acid with 2 ml. of concentrated hydrochloric acid; after standing 4 days at room temperature, 20 ml. of water was added and the pH adjusted to neutral with sodium bicarbonate. The small amount of insoluble which remained was removed and the filtrate evaporated to dryness. The residue was extracted twice with 30 ml. portions of boiling 95% ethanol; the combined extracts were cooled to 25°, filtered, then cooled for several days at 5°. Almost colorless crystals of the first compound slowly formed; they were removed, washed with cold ethanol, then ether, and dried. Addition of ether to the mother liquors until a permanent turbidity developed, followed by further cooling gave more of the same compound; the filtrate was saved (see below). A solution of this solid in water was only very weakly fluorescent (probably contamination by the following compound); ¹H nmr (deuterium oxide, 100 MHz): δ 1.20 (d, 3H, 4-CH₃, J = ~6.5 Hz), 1.25 (d, 3H, 2-CH₃, J = ~6.5 Hz), 1.45 (dd, 1H, H_{3a}, J_{3a3b} = 13.5 Hz, J_{3aHx} = 11 Hz), 2.04 (dt, 1H, H_{3b}, J_{3a3b} = 13.5 Hz, J_{3bHx} = J_{3bHy} = 4 Hz), 2.67 (m, 1H, H₄), 3.58 (m, 1H, H₂), 3.87 (d, 1H, H_c, J_{HcHd} = 18 Hz), 4.07 (d, 1H, H_d, J_{HcHd} = 18 Hz), 6.75 (q, 1H, H_e, J_{CF₃-H_e} = 1.6 Hz), 7.31 (s, 1H, H₅).

Anal. Calcd. for C₁₆H₁₅F₃N₂O₅·H₂O: C, 44.04; H, 3.93; F, 13.06; N, 6.42. Found: C, 44.80; H, 3.99; F, 12.86; N, 6.42, 6.35.

The alcohol-ether mother liquors from above were evaporated; the residue was slurried with 10 ml. of 2-propanol, filtered, and the filtrate treated with 50 ml. of ether. The off-white solid which precipitated was removed and dried. An aqueous solution fluoresced at 498 nm (excited 400 nm); ¹H nmr (deuterium

oxide, 100 MHz): δ 1.17 (d, 3H, 6-CH₃, J = 6.5 Hz), 1.28 (d, 3H, 8-CH₃, J = 6.5 Hz), 1.40 (m, 1H, H_{7a}, J_{7a7b} = 14 Hz), 2.04 (m, 1H, H_{7b}, J_{7a7b} = 14 Hz), 2.66 (m, 1H, H₆), 3.74 (m, 1H, H₈), 4.00 (d, 1H, H_c, J_{HcHd} = 17.5 Hz), 4.51 (d, 1H, H_d, J_{HcHd} = 17.5 Hz), 6.28 (s, 1H, H₃), 7.29 (q, 1H, H₅, J_{CF₃-H₅} = 1.5 Hz).

The result was essentially the same when some of the ethyl ester was hydrolyzed in 80% sulfuric acid at 25°. Quenching in ice, followed by neutralization with sodium bicarbonate and isolation as above, gave largely the non-fluorescing substituted crotonate.

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- (1) Author to whom correspondence should be addressed.
- (2) Present address, University of California, Lawrence Livermore Laboratory, L-215, Livermore, CA 94550.
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