was heated at 95–100 °C for a few hours. Similarly, no reaction occurred when the acid chloride saturated with boron fluoride was allowed to stand at ambient temperature for 4 days.

Reaction of Fluorodinitroethoxyacetyl Chloride with Triethylamine. To a stirred and cooled (0–5 °C) solution of 2.3 g (0.01 mol) of fluorodinitroethoxyacetyl chloride[7] in 70 ml of diethyl ether was added dropwise (15 min) a solution of 1.0 g (0.01 mol) of triethylamine in 15 ml of diethyl ether. A white, crystalline solid precipitated instantaneously. The mixture, protected from moisture by a calcium chloride drying tube, was refluxed for 24 h, cooled, and filtered. The filter cake, washed with ether, amounted to ca. 3 g. The filtrate and washings were combined and evaporated on a rotary evaporator, leaving no residue.

Registry No.—Fluorodinitroethoxyacetic anhydride, 58815-88-6; fluorodinitroethoxyacetic acid, 25172-22-9; fluorodinitroethoxymethyl fluorodinitroethoxyacetate, 58815-89-7; fluorodinitroethoxymethyl acetate, 50836-79-8; fluorodinitroethoxyacetyl chloride, 25172-23-0; aluminum chloride, 7446-70-0; triethylamine, 121-44-8.

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Bromination of 1-Alkyl-3-methyl-2-pyridones with *N*-Bromosuccinimide

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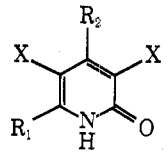
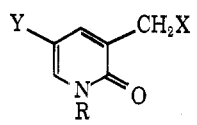
The functionalization of a β-methyl group attached to a pyridine or quinoline ring has proven to be an important step in several approaches to the synthesis of camptothecin[1,2,3] and bromination with *N*-bromosuccinimide (NBS) met with only limited success. With the pyridine derivatives no bromination of the ring or alkyl substituent occurred unless the basicity of the nitrogen was decreased by an electronegative, α substituent.[1,4] With 6-methyl- or 4,6-dimethyl-2-pyridone (1 or 2) NBS caused ring bromination to 3 and 4 rather than substitution of the methyl groups even using benzoyl peroxide as catalyst.[5,6] The earlier report[7] that 1,3-dimethyl-2-pyridone (5) gave bromination of the 3-methyl group with NBS to give 6 was recently questioned, for ring bromination to give 7 was confirmed as the product from this reaction.[3]



1, $R_1 = CH_3$; $R_2 = X = H$
2, $R_1 = R_2 = CH_3$; $X = H$
3, $R_1 = CH_3$; $R_2 = H$; $X = Br$
4, $R_1 = R_2 = CH_3$; $X = Br$



5, $R = CH_3$; $X = Y = H$
6, $R = CH_3$; $X = Br$; $Y = H$
7, $R = CH_3$; $X = H$; $Y = Br$
8, $R = PhCH_2$; $X = Y = H$
9, $R = PhCH_2$; $X = H$; $Y = Br$
10, $R = PhCH_2$; $X = Br$; $Y = H$

Since 1-substituted 3-bromomethyl-2-pyridone would be a convenient intermediate the NBS reaction with 1-alkyl-3-methyl-2-pyridones (5 and 8) was reinvestigated. A dilute solution of 1-benzyl-3-methyl-2-pyridone (8) was treated with NBS and dibenzoyl peroxide in refluxing carbon tetrachloride for 50 min and a solid product remained after filtration and evaporation of the solvent. The NMR spectrum of the product showed the triplet at 6.17 ppm due to the aromatic 5 proton, but the singlet at 2.16 ppm due to the signal for the *C*-methyl was missing. A new singlet was evident at 4.47 ppm due to a bromomethylene group. The elemental analyses confirmed that bromination of the methyl group had occurred to give 10. A careful analysis of the NMR spectrum showed the presence of a trace of starting compound 8 but there were no signals which could be assigned to 9. The reaction was repeated using the concentration of reagents previously reported to give ring bromination of 5[3] and again the major product was the bromomethyl derivative 10 with only 20–30% of the ring brominated product 9 detectable by NMR. Indeed a reasonable yield of ring bromination of 8 could be obtained only by a reaction with NBS in the *absence* of dibenzoyl peroxide. In benzene or carbon tetrachloride the NMR of the crude product showed the presence of only about 10% of the bromomethyl derivative 10.

The reactions were repeated with 1,3-dimethyl-2-pyridone (5) and NBS, in the absence of dibenzoyl peroxide or with this catalyst in a concentrated reaction mixture, and gave 7 as the major product by ring bromination. The crude products contained about 10% unreacted 5 and 10% of the 3-bromomethyl-1-methyl-2-pyridine (6) detected by NMR analysis. The reaction of 5 with NBS and dibenzoyl peroxide after an eightfold dilution gave mainly side-chain bromination to form 6 contaminated with only a few percent of starting material or product of ring bromination, 7.

The ring or chain bromination of 1-alkyl-3-methyl-2-pyridones with NBS can be controlled in two examples to give either ring or side chain substitution. In the absence of dibenzoyl peroxide as a catalyst, NBS gave bromination of the ring in the same manner as would be expected with molecular bromine. In the presence of dibenzoyl peroxide, dilute reaction conditions gave side chain bromination with NBS. In concentrated reaction mixtures significant yields of ring bromination occurred even in the presence of dibenzoyl peroxide. The 1-methyl derivative, 5, was more sensitive to this concentration effect than was the 1-benzyl-3-methyl-2-pyridone (8). By a proper choice of reaction conditions selectivity could be controlled to give crude products which crystallized and whose NMR analyses showed less than 10% contamination by the isomeric bromination product.

Experimental Section

1-Benzyl-3-methyl-2-pyridone (8). To a solution of 6.44 g of 87% KOH in 150 ml of absolute ethanol at 50 °C was added 3-methyl-2-pyridone.[8] The resulting solution was stirred for 20 min before the dropwise addition of benzyl chloride. The mixture was stirred at 50 °C for 3 h, concentrated under reduced pressure, poured into 180 ml of water, and extracted with chloroform (3 × 50 ml). The organic phase was washed with water and saturated salt solution, dried ($MgSO_4$), filtered, and concentrated to yield a light yellow oil which crystallized under pentane with cooling. The solid was collected and dried to give 15.75 g (86%) of 8 as white crystals, mp 69–71 °C. The product was recrystallized twice from petroleum ether (bp 30–60 °C)–methylene chloride to afford an analytical sample of 8: mp 70.5–71.5 °C; NMR ($CDCl_3$) δ 7.12–7.48 (m, including s at 7.36, 7 H total), 6.06 (t, 1 H), 5.15 (s, 2 H), 2.16 (s, 3 H); ir (KBr) 1645 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.34; H, 6.78; N, 7.11.

1,3-Dimethyl-2-pyridone (5). Using the procedure above, 6.94 g (63.6 mmol) of 3-methyl-2-pyridone and 13.0 g (91.6 mmol) of methyl iodide gave after vacuum distillation 6.63 g (85%) of 1 as a clear oil: bp 63 °C (0.05 mm) [lit.[8] bp 83–84 °C (1.3 mm)]; NMR ($CDCl_3$) δ 7.24–7.50 (m, 2 H), 6.16 (t, 1 H), 3.60 (s, 3 H), 2.16 (s, 3 H); ir (neat) 1650 cm^{-1}.

1-Benzyl-5-bromo-3-methyl-2-pyridone (9). A solution of 1.0 g (5.02 mmol) of **8** in 10 ml of dry benzene was placed in a dry, nitrogen-filled flask. To the solution was added 0.90 g (5.02 mmol) of NBS and the mixture was heated at 90 °C for 50 min. The benzene was removed under reduced pressure, 25 ml of carbon tetrachloride was added to the residue, and the resulting mixture was filtered. The filter cake was washed with 25 ml of carbon tetrachloride and the filtrate was concentrated under reduced pressure leaving an orange oil as residue, the NMR of which showed less than 10% of **10**. The oil crystallized on cooling, and trituration with 10 ml of anhydrous ether gave 0.95 g (68%) of crude **9** as a white solid, mp 86.5–89 °C. The solid was recrystallized twice from ether to give an analytical sample of **9**: mp 96.5–97.5 °C; NMR ($CDCl_3$) δ 7.04–7.60 (m, including s at 7.23, 7 H total), 5.02 (s, 2 H), 2.12 (s, 3 H).

Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04. Found: C, 55.98; H, 4.56; N, 5.00.

The reaction in 10 ml of carbon tetrachloride gave identical results. The product crystallized and NMR of the crude solid showed about 10% of **10**.

1-Benzyl-3-bromomethyl-2-pyridone (10). In a 100-ml flask equipped with a reflux condenser and a drying tube was placed a solution of 1.0 g (5.02 mmol) of **8** in 75 ml of dry carbon tetrachloride. To the solution was added 0.90 g (5.02 mmol) of NBS and 0.1 g of dibenzoyl peroxide. The mixture was heated under reflux with a 100-W lamp for 4 h.[12] After this time the mixture was cooled and filtered, and the solvent was removed to afford a yellow oil which solidified on cooling under 15 ml of anhydrous ether to give 1.0 g (72%) of crude **10**, mp 86–90 °C, the NMR spectrum of which showed no product of ring bromination, **9**. The solid was recrystallized twice from ether to give an analytical sample of **10**: mp 101–101.5 °C; NMR ($CDCl_3$) δ 7.30–7.60 (m, including s at 7.34, 7 H total), 6.17 (t, 1 H), 5.17 (s, 2 H), 4.47 (s, 2 H).

Anal. Calcd for $C_{13}H_{12}BrNO$: C, 56.14; H, 4.35; N, 5.04. Found: C, 56.23; H, 4.43; N, 4.94.

The reaction was repeated using only 10 ml of carbon tetrachloride and the NMR of the crude solid showed the presence of 20–30% of **9**.

3-Bromomethyl-1-methyl-2-pyridone (6). In a dry nitrogen-filled 250-ml flask was placed a solution of 0.83 g (6.7 mmol) of **5** in 100 ml of dry carbon tetrachloride. To the solution was added 1.19 g (6.7 mmol) of purified NBS[9] and 0.15 g of dibenzoyl peroxide. The mixture was heated under reflux for 1 hr. After this time the mixture was cooled and filtered, and the solvent removed. The solid residue[10] was stirred under 10 ml of anhydrous ether and was removed by filtration to afford 0.85 g (63%) of **6** as tan crystals, mp 86–89 °C. The product was recrystallized twice from benzene to give an analytical sample of **6**: mp 101–101.5 °C (lit.[7] mp 98–99 °C); NMR ($CDCl_3$) δ 7.67 (m, 2 H), 6.31 (t, 1 H), 4.58 (s, 2 H), 3.65 (s, 3 H).

Anal. Calcd for C_7H_8BrNO: C, 41.61; H, 3.99; N, 6.93. Found: C, 41.68; H, 4.06; N, 6.83.

5-Bromo-1,3-dimethyl-2-pyridone (7). A solution of 0.83 g (6.7 mmol) of **5** in 12 ml of dry carbon tetrachloride was placed in a dry nitrogen-filled flask. To the solution was added 1.18 g (6.6 mmol) of purified NBS[9] and the mixture was heated under reflux for 30 min. After this time 25 ml of carbon tetrachloride was added; the mixture was cooled and filtered; and the solvent was removed to afford 1.28 g (96%) of **7** as a light-yellow solid,[11] mp 98–101 °C. Recrystallization of the product from petroleum ether (bp 30–60 °C) gave fluffy, white crystals: mp 105–106 °C (lit.[3] mp 106–107 °C); NMR ($CDCl_3$) δ 7.30–7.55 (m, 2 H), 3.61 (s, 3 H), 2.20 (s, 3 H).

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Registry No.—**5**, 6456-92-4; **6**, 58802-10-1; **7**, 51417-13-1; **8**, 58802-11-2; **9**, 58802-12-3; **10**, 58802-13-4; 3-methyl-2-pyridone, 1003-56-1; benzyl chloride, 100-44-7; methyl iodide, 74-87-3; *N*-bromosuccinimide, 128-08-5.

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(9) The NBS was purified by recrystallization from ten times its weight of water and drying under vacuum overnight (mp 182.5–184 °C).
(10) The residue contained less than 10% of compounds **5** and **7**, combined, by NMR.
(11) The product contained only a trace (<2%) of compounds **5** and **6** by NMR.
(12) The manner and the time of heating after 50 min is not critical.

Biological Probes. 3. Methods for Carbon-4 and Carbon-5 Labeling in Nicotinamide

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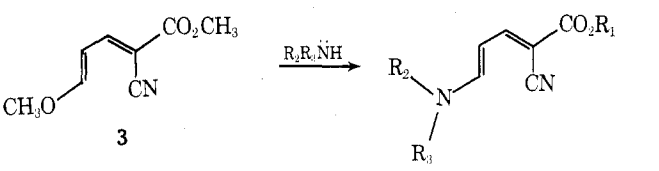
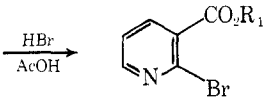
Increased interest in nonradioactive labels for use as general biological probes had led us to develop efficient methods for labeling the nicotinamide (**1**) portion of NAD^+ (**2**).[1-3] We have described facile pyridine syntheses in which nicotinamide can be labeled (^{13}C, ^2H, ^{15}N) at the 1, 2, 3, 6, and carbonyl positions and then be biosynthetically incorporated into the coenzyme NAD^+.[4] However, these methods were not useful for labeling the 4 position of the nicotinamide ring, the site at which biological oxidation–reduction occurs in NAD^+. We now wish to report an efficient, high-yield procedure for label incorporation (^{13}C, ^2H) at the 4 and also the 5 position of nicotinamide (**1**).

Prior experience with diene **3** as a labeled pyridine precursor suggested an attractive synthetic route to **1**. Our initial studies focused on modification of diene **3** with designs on making this general type of synthon more accessible from lower molecular weight, labeled starting materials. Specifically, diene **3** readily undergoes addition (1,6) of amines with loss of methanol forming butadienamines, such as **4**. These conjugated enamines (**4**), analogous to diene **3**, undergo acid-catalyzed (HBr/AcOH) cyclization to 2-bromonicotinate **5** in high yield.



3 **4a**, $R_1 = R_2 = Me$; $R_3 = C_6H_5$
b, $R_1 = R_2 = R_3 = Me$
c, $R_1 = Et$; $R_2 = R_3 = Me$



5, R = Me or Et

Therefore, several routes to **3** or **4** were investigated with our labeling goals in mind resulting in the preparation of enamine **4c** as shown in Scheme I.