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A ONE-STEP CONVERSION OF ISOQUINOLINIUM SALTS INTO NAPHTHALENE DERIVATIVES[1]

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Abstract—Berberine chloride (**1**) upon treatment with NaOAc–Ac_2O yields naphthalene derivatives **4** and **5**. In like fashion, **8** gives naphthalene **10**; isoquinoline methiodide leads to β-naphthyl acetate; and **12** provides **14**. The reaction has been extended to the 3-carbonyl pyridinium series where 3-acetylpyridine methiodide and 3-pyridinecarboxaldehyde methiodide furnish lactones **16** and **17**, respectively. All these transformations proceed by initial nucleophilic attack of the acetic anhydride anion on the immonium carbon atom.

It had previously been established that 3,4-dihydroisoquinolinium salts can undergo ring opening between C-1 and N-2 under Schotten–Baumann conditions with formation of an aldehydo amide. In that transformation, hydroxide anion acted as the nucleophile while benzoyl chloride was the N-benzoylating agent.[3]

Presently, an effort to extend this reaction to the quaternary alkaloid berberine (**1**) which incorporates an isoquinolinium system in rings C and D gave instead the unstable pseudobase **1a** which reverts to berberine. Since berberine had never previously been cleaved at the N-7 to C-8 bond, it was decided to investigate the reaction of this salt with sodium acetate in acetic anhydride.

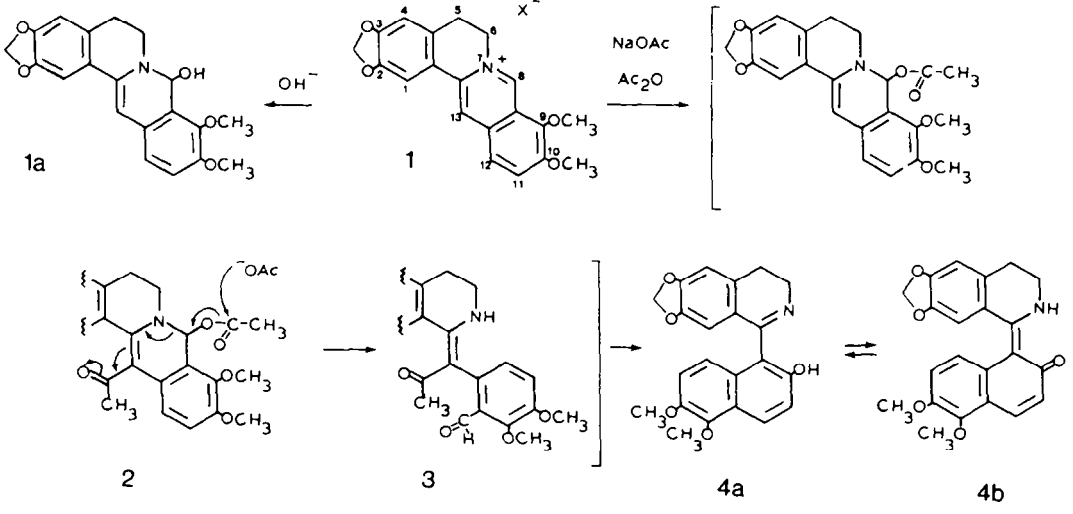
After heating berberine chloride (**1**) with sodium acetate in acetic anhydride at 110–115° for 48 hr, two major products were separated. The principal produce (39%) was characterized as the 1-(α-naphthyl)-isoquinoline **4** which crystallized from ethanol in nearly colorless plates of **4a**.[4] The molecular formula for this base, $C_{22}H_{19}NO_5$, indicated that two extra C atoms had been incorporated into the original salt. The compound readily dissolved in chloroform to generate a red solution due to contribution of the tautomeric form **4b**. The most notable features of the NMR spectrum in $CDCl_3$ were an AB quartet (2H) centered at δ 7.66 representing the 3′ and 4′ protons in **4b**, as well as a broad NH singlet (1H) at δ 8.85.

Initially, we considered that formation of the 1-(α-naphthyl)isoquinoline **4** could be rationalized through the steps indicated in Scheme 1.

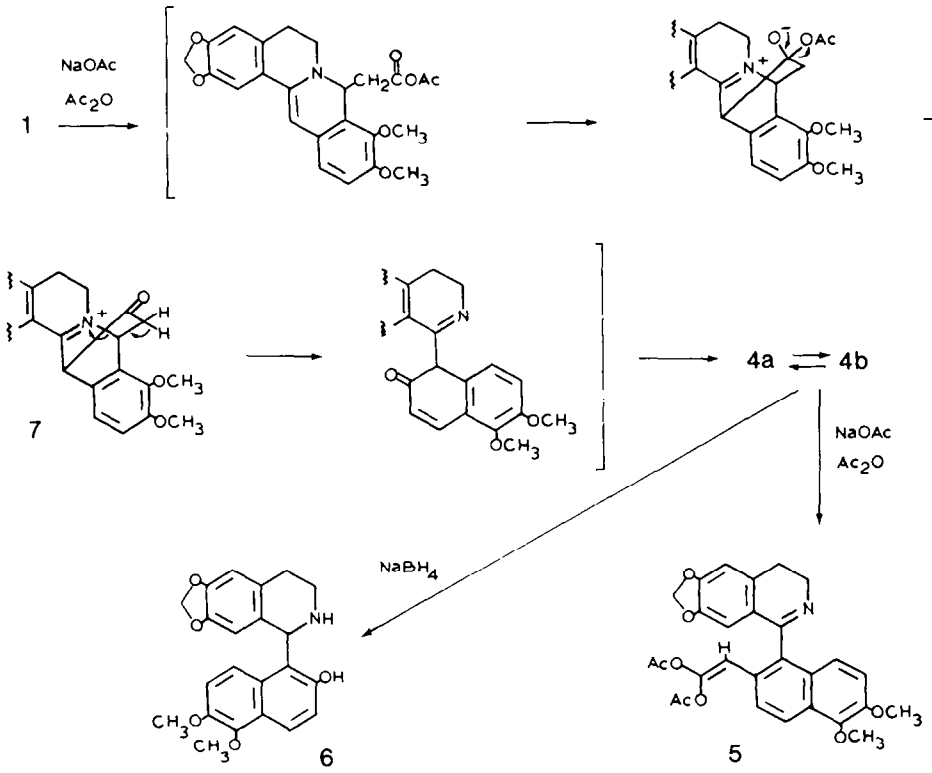
The berberinium cation undergoes nucleophilic attack by acetate at C-8, and the resulting 0-acetylated pseudobase can suffer enamine acylation at C-13 to provide the intermediate **2**. At this stage a second mole of acetate ion attacks the C-8 acetate function to give rise to the open aldehydo vinylogous amide **3**. Intramolecular aldol condensation then results in formation of the 1-(α-naphthyl)isoquinoline **4**.

However, a more attractive mechanism for the generation of **4** is outlined in Scheme 2. Nucleophilic attack of acetic anhydride anion at C-8 of berberine followed by an internal enamine acylation leads to the bridged intermediate **7**. β-Elimination of the quaternary nitrogen then results in cleavage of the N-7–C-8 bond with formation of a species which isomerizes to **4**. This bridge mechanism is supported by the finding that berberine does not react when treated with sodium benzoate and benzoic anhydride, or with sodium trifluoroacetate and trifluoroacetic anhydride.

The minor product (24%) from the reaction of ber-



Scheme 1.



Scheme 2.

berine with sodium acetate in acetic anhydride proved to be the bright yellow diacetate **5**, $C_{28}H_{25}NO_8$. The NMR ($CDCl_3$) of this compound exhibits a singlet at δ 2.02. (6H) assignable to the two acetate Me groups. An additional singlet (1H) at δ 6.95, which was conspicuously absent in the NMR spectrum of **4**, could be ascribed to the vinylic proton in the side chain. This minor product must be formed by further condensation of **4** with acetic anhydride (Scheme 2); and indeed treatment of **4** with sodium acetate in acetic anhydride produced the diacetate **5**. The 1-(α-naphthyl)isoquinoline **4** could also be reduced in quantitative yield with $NaBH_4$ in methanol to the tetrahydroisoquinoline derivative **6** (Scheme 2).

The known aromatic protoberberinium salt 2,3,10,11 - tetramethoxydibenzo[a,g]quinolizinium chloride (**8**),[5,6] readily available from papaverine, was next investigated. This salt presents an interesting situation since, following initial attack by the nucleophile at C-8, enamine acylation may occur *a priori* either at C-5 or at C-13. In fact, only one product could be obtained from **8** after heating in sodium acetate and acetic anhydride, namely the 1 - (α - naphthyl)isoquinoline acetate **10**, isolated in 70% yield. The salient features of the NMR spectrum of this product include an acetate Me resonance at δ 1.73, and two AB quartets centered at δ 7.44 and 8.00 which represent the two sets of ortho aromatic protons in the molecule. The initially formed phenolic naphthylisoquinoline **9** must undergo O-acetylation to the product **10**. No keto-enol tautomerization analogous to the **4a–4b** equilibrium was observed.

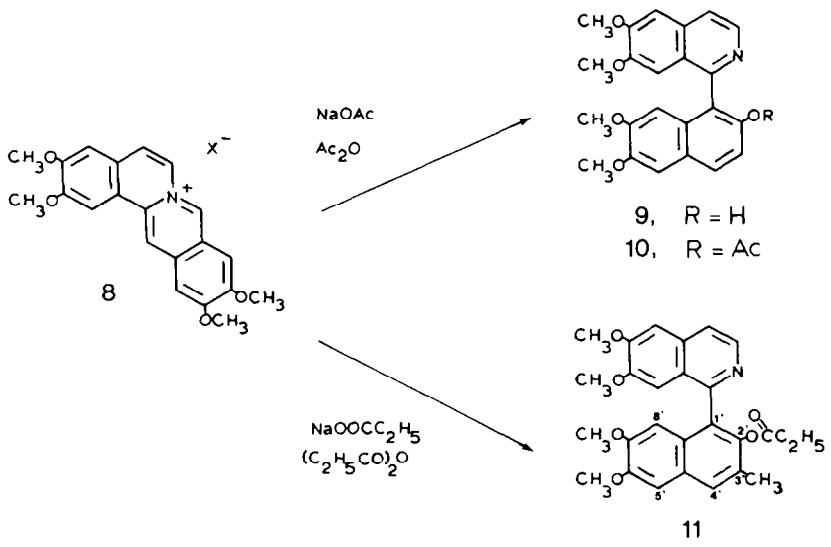
The above transformations are not limited to the use of sodium acetate in acetic anhydride. Thus when the protoberberinium salt **8** was heated in the presence of sodium propionate in propionic anhydride, the product was the 1-(α-naphthyl)isoquinoline propionate ester **11** obtained in 75% yield. The NMR spectrum of this ester incorporates an aromatic C-3' methyl singlet at δ 2.19, while the H-4' aromatic proton appears as a singlet at δ 7.58.

An interesting extension of the above reactions proved to be the one-step conversion of the methiodide salt of isoquinoline itself into β-naphthyl acetate. Treatment of isoquinoline methiodide with sodium acetate in acetic anhydride resulted in formation of β-naphthyl acetate in 15% yield, as indicated in Scheme 3 where a bridge mechanism is used to rationalize the formation of the product.

The reaction of benzo[b]quinolizinium bromide (**12**)[7] with sodium acetate in acetic anhydride was also studied. The product, obtained in 61% yield, proved to be the tricyclic ester 1 - (2'-pyridyl) - 2 - naphthyl acetate (**14**), formed through the intermediacy of the tetracyclic ketone **13**. Our belief that a bridge mechanism is indeed operative is reinforced by the extensive work of Fields *et al.* in the diene condensations of substituted isoquinolinium salts.[8] In particular, they established that salt **12** readily undergoes Diels–Alder addition with ketene diethyl acetal to the bridged species **15** which upon mild acid hydrolysis yields ketone **13**. Treatment of **13** with sodium acetate and acetic anhydride then furnished the tricyclic ester **14**.

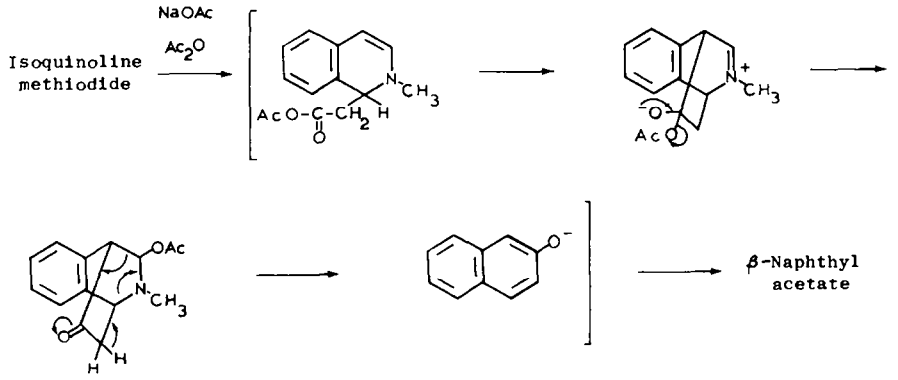
To summarize, the transformation of isoquinolinium salts into naphthalene derivatives can be achieved using as reagents the salt of a simple aliphatic carboxylic acid together with its corresponding anhydride. The yields will vary depending upon the nature of the starting isoquinolinium salt. The above conversion of berberine (**1**) to the naphthyl derivatives **4** and **5** represents the first fully authenticated direct opening of ring C of this alkaloid.

In order to gain further insight into the reaction

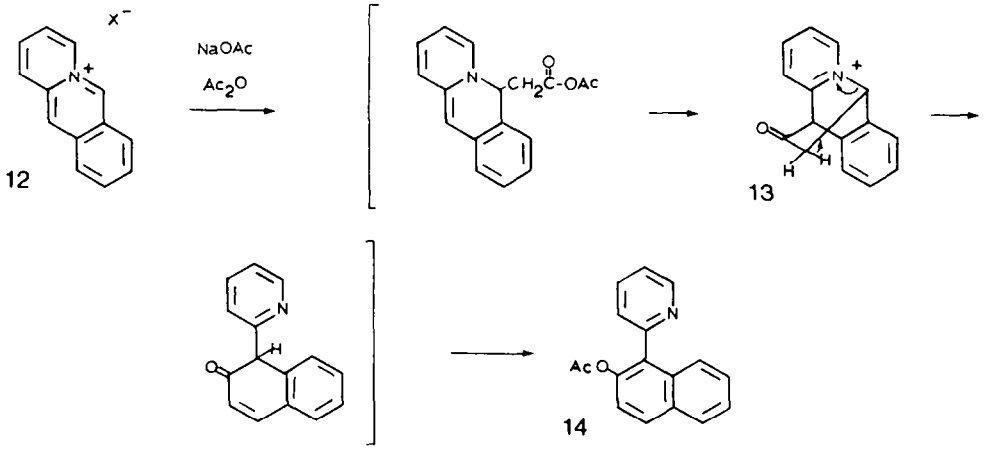


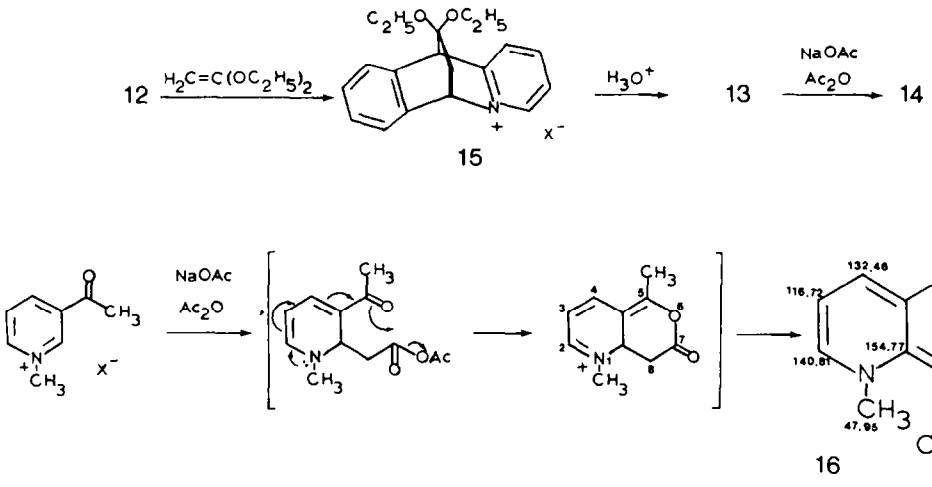
mechanism, 3-acetylpyridine methiodide was refluxed with sodium acetate and acetic anhydride. The product was a complex mixture from which a bright yellow solid, $C_{12}H_{13}NO_3$, could be isolated in 15% yield after chromatography. The most prominent features of the PMR spectrum of this material are a CH_3–CH doublet at δ 1.71, a Me ketone singlet at δ 2.55, and an enamine N–Me singlet at 3.80. That the yellow material is represented by expression **16** is supported not only by the PMR data, but also by the IR spectrum which shows two conjugated CO peaks at 1585 and 1677 cm $^{-1}$. Final confirmation of structure **16** was forthcoming from the C-13 NMR spectrum obtained in $CDCl_3$ which is summarized below. Formation of this product can be rationalized by initial attack of the acetic anhydride anion on the immonium bond of the starting pyridinium salt.

In like fashion, 3-pyridinecarboxaldehyde methiodide led to a small yield of a yellow crystalline compound formulated as **17**. Under identical experimental con-

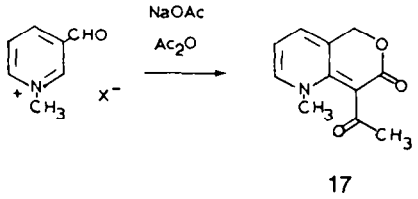


Scheme 3.





ditions, both pyridine methiodide and lutidine methiodide failed to react. A C-3 CO function is, therefore, required for reaction of a pyridinium salt.



Initiation of the reaction by the acetic anhydride anion attack at the immonium carbon of the simple 3-CO pyridinium salts is mirrored in the conversion of the more complex isoquinolinium salts into naphthalene derivatives as delineated in Schemes 2 and 3.

EXPERIMENTAL

Standard experimental procedures. Microanalyses are by Midwest Microlab, Inc., Indianapolis. M.ps are uncorrected. The PMR data is at 60 MHz in $CDCl_3$; and TMS was the internal standard. The CMR spectrum of **16** was obtained using a JEOL PFT-100 spectrometer. The carbon chemical shifts are in ppm relative to TMS. Mass spectra were collected on an AEI MS-902 spectrometer. All TLC was on Merck Silica Gel-254 plates.

Reaction of berberine with NaOAc *and* Ac_2O. A mixture of **1** chloride (1.00 g; 2.69 mmol) and anh NaOAc (2.50 g) in Ac_2O (15 ml) was stirred at 110–115° for 48 hr under N_2. After the dark brown mixture was allowed to stand for 5 hr at room temp., the solid material was filtered off. Concentration of the filtrate *in vacuo* afforded a dark oil which was chromatographed over silica gel. Elution with $CHCl_3$ supplied 0.30 g (24%) of the yellow vinyl diacetate (**5**), m.p. 207–208° (EtOH); PMR δ2.02 (6 H, s, $2\,CH_3CO$), 2.22–3.75 (4 H, m, CH_2–CH_2), 3.88 and 3.97 (2×3H, 2s, $2\,OCH_3$), 6.07 (2H, broad d, J = 3 Hz, OCH_2O), 6.30 (1H, s, ArH); 6.74 (1H, s, ArH), 6.95 (1H, s, HC=C), 7.05 (2H, s, ArH), 7.87 (2H, q, J = 9 Hz, ics = 55 Hz); $\nu_{max}^{CHCl_3}$ 1723 (broad, C=O); λ_{max}^{EtOH} 236, 260 sh, 267, 297 sh, 324 and 382 nm (log ϵ 4.87, 4.45, 4.49, 4.18, 4.05 and 4.03). (Found: C, 66.76; H, 4.99. Calc. for $C_{28}H_{25}NO_8$: C, 66.79; H, 5.00%).

Elution of the column with a 5% MeOH in $CHCl_3$ soln yielded a major component. Recrystallization from EtOH afforded 0.394 g (39%) of **4** as off-white crystals, m.p. 216–218°. PMR δ2.50–3.80 (4H, m, CH_2–CH_2), 3.90 and 4.00 (2×3H, 2s, $2\,OCH_3$), 5.90 (2H, q, J = 1 Hz, OCH_2O), 6.37, 6.77 (2×1H, 2s, 2 ArH), 6.98 (2H, s, ArH), 7.66 (2H, q, J = 10 Hz, ics = 52 Hz, ArH), 8.85 (1H, broad s, NH); $\nu_{max}^{CHCl_3}$ 1625 (C=O), 1600 cm^{-1} (arom); λ_{max}^{EtOH} 233, 270, 278, 291 sh, 320 and 362 sh (log ϵ 5.06, 4.09, 4.17, 4.06, 4.11 and 3.82). (Found: C, 70.42; H, 5.22. Calc. for $C_{22}H_{19}NO_5$: C, 70.02; H, 5.07%). High res. ms M^+ *m/e* 377.1251; calc. 377.1262.

$NaBH_4$ *Reduction of* **4**. To a methanolic soln of **4** (0.10 g) was added 0.05 g $NaBH_4$. The red color of the soln disappeared, and a white solid precipitated. After filtering and washing with MeOH, 0.10 g (99%) of colorless **6** was obtained, m.p. 150° (EtOH); λ_{max}^{EtOH} 270 280, 290 and 345 nm (log ϵ 3.94, 4.01, 3.92 and 3.46). (Found: C, 67.48; H, 5.90. Calc. for $C_{22}H_{21}NO_5{\cdot}C_2H_5OH$: C, 67.75; H, 6.35). High res. ms M^- *m/e* 379.1406; calc. 379.1419.

Reaction of **4** *with* NaOAc *and* Ac_2O. A mixture of **4** (0.10 g; 0.265 mmol) and anh NaOAc (0.250 g) in Ac_2O (5 ml) was stirred at 110° for 24 hr under N_2. The mixture was allowed to stand overnight at room temp., and the solid was filtered off. Concentration of the filtrate *in vacuo* gave a dark residue which was chromatographed on 0.5 mm silica gel plates using a 5% MeOH in $CHCl_3$ soln. The major component was collected to yield 0.071 g (53%) of a yellow solid, m.p. 206–207°, which was identical in all respects with **5**.

Reaction of **8** *with* NaOAc *and* Ac_2O. A mixture of **8** chloride[5,6] (0.25 g; 0.715 mmol) and anh NaOAc (0.625 g) in 10 ml Ac_2O was heated near 110° for 36 hr under N_2. After cooling, the solid material was filtered and washed with Ac_2O. Removal of the solvent under reduced pressure gave a dark residue which was chromatographed over silica gel. Elution with $CHCl_3$ provided 0.22 g (70%) of **10** as an oil. Trituration with ether gave a white solid, m.p. 102–104°, which slowly turned yellow in the atmosphere. PMR δ 1.73 (3H, s, CH_3CO), 3.53, 3.61, 3.88 and 3.90 (4×3H, 4s, $4\,OCH_3$), 6.51 (1H, s, H-8), 6.78 (1H, s, H-5), 7.07 (1H, s, H-8'), 7.14 (1H, s, H-5'), 7.44 (2H, q, J = 8.5 Hz, ics = 34 Hz, H-3' and H-4'), 8.00 (2H, q, J = 5.5 Hz, ics = 61 Hz, H-3 and H-4); λ_{max}^{EtOH} 234, 313 sh and 326 nm (log ϵ 5.14, 4.00 and 4.07). Low res. ms *m/e* 433 (M^+), 418, 391 (base), and 376. The analytical sample was prepared from the naphthol **9**, m.p. 234–235° (benzene), obtained by hydrolysis of the acetate **10**. (Found: C, 71.45; H, 5.95. Calc. for $C_{23}H_{21}NO_5{\cdot}C_6H_6$: C, 71.34; H, 5.49%). High res. ms of **9** M^+ *m/e* 391.1415; calc. 391.1418.

Reaction of **8** *with sodium propionate and propionic anhydride.* A mixture of **8** (0.50 g; 1.43 mmol) and anh sodium propionate in 10 ml of propionic anhydride was heated at 105° for 48 hr under N_2. The dark suspension was cooled and filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed over silica gel. Elution of the column with a 1% MeOH in $CHCl_3$ soln yielded 0.49 g (73%) of the oily ester **11**. The oil was triturated with petroleum ether to give a white solid, m.p. 105–108° ($CHCl_3$). PMR δ0.65 (3H, t, J = 7.5 Hz, CH_3CH_2C=O), 2.02 (2H, q, J = 7.5 Hz, CH_3CH_2C=O), 2.19 (3H, s, Ar–CH_3), 3.51, 3.63, 3.86 and 3.88 (4×3H, 4s, $4\,OCH_3$), 6.42 (1H, s, H-8), 6.85 (1H, s, H-5), 7.10 (2H, s, H-5' and H-8'), 7.58 (1H, s, H-4'), 8.02 (2H, q, J = 5.5 Hz, ics = 59 Hz, H-3 and H-4); $\nu_{max}^{CHCl_3}$ 1754 (C=O), 1621 cm^{-1} (arom); λ_{max}^{EtOH} 237, 314 and 328 nm (log ϵ 5.00, 3.83 and 3.97). (Found: C, 67.33; H, 5.71. Calc. for $C_{27}H_{27}NO_6{\cdot}1/3CHCl_3$: C, 67.54; H, 5.65%). High res. ms M^- *m/e* 461.1822; calc. 461.1837.

Reaction of isoquinolinium methiodide with NaOAc *and* Ac_2O. A mixture of isoquinoline methiodide (1.00 g; 3.69 mmol) and NaOAc (2.50 g) in 15 ml of Ac_2O was stirred at 115° for 48 hr under N_2. After allowing the mixture to cool, the product was filtered through a sintered glass funnel. Concentration of the filtrate left a dark viscous oil which was chromatographed over silica gel. Elution with $CHCl_3$ yielded 0.06 g of an off-white solid, m.p. 56–58°, which exhibited physical and spectral properties identical with β-naphthyl acetate. Further elution of the column with a 20% MeOH in $CHCl_3$ afforded 0.422 g of unreacted isoquinoline methiodide. The yield of β-naphthyl acetate was 15% based on recovered methiodide salt.

Reaction of **12** *with* NaOAc *and* Ac_2O. A mixture of **12** bromide (1.00 g; 3.84 mmol) and anh NaOAc (2.50 g) in Ac_2O (15 ml) was heated at 72° for 24 hr under N_2. After cooling, the solid material was filtered off and washed with Ac_2O. Removal of the solvent gave a brown residue which was chromatographed on silica gel. Elution with $CHCl_3$ and recrystallization from ether provided colorless plates of **14**, m.p. 114.5–115°(ether), lit. 113–114°,[8] 0.614 g (61%). PMR δ1.97 (3H, s, CH_3CO), 7.25 (6H, m, H3–H8), 7.65 (3H, m, H3',4',5'), 8.55 (1H, d, J = 5 Hz, H6'); $\nu_{max}^{CHCl_3}$ 1760 (C=O). (Found: C, 77.58; H, 4.90; N, 5.29. Calc. for $C_{17}H_{13}NO_2$: C, 77.56; H, 4.90; N, 5.26%). High res. ms M^+ 263.0953. Calc. 263.0946.

Reaction of 3-acetylpyridine methiodide with NaOAc *and* Ac_2O. A mixture of the methiodide (1.00 g; 3.80 mmol) and anh NaOAc anh NaOAc (2.50 g) in 15 ml Ac_2O was heated at 105° for 48 hr under N_2. After cooling, the solid material was filtered off and washed with Ac_2O. Removal of the solvent left a brown residue which was chromatographed on silica gel. Elution with 10% MeOH in $CHCl_3$ afforded **16** as bright yellow crystals, m.p. 221–222.5° ($CHCl_3$), 0.125 g, 15%; PMR δ 1.71 (3H, d, J = 6.5 Hz, CH_3CH), 2.55 (3H, s, CH_3CO), 3.80 (3H, s, N–CH_3), 5.07(1H, q, J = 6.5 Hz, CH_3CH), 7.06 (1H, t, J = 7 Hz, H3), 7.60 (1H, d, J = 7 Hz, H4), 7.96 (1H, d, J = 7 Hz, H2); $\nu_{max}^{CHCl_3}$ 1585 and 1677 cm^{-1} (C=O); λ_{max}^{EtOH} 260, 303 and 377 nm (log ε 4.07, 3.83 and 4.05). (Found: C, 65.72; H, 6.21. Calc. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.97%). High res. ms M^+ *m/e* 219.0899. Calc. 219.0895.

Reaction of 3-pyridinecarboxaldehyde methiodide with NaOAc *and* Ac_2O. A mixture of the methiodide (1.00 g; 4.02 mmol) and anh NaOAc (2.50 g) in 15 ml Ac_2O was heated at 90° for 44 hr under N_2. After cooling, the solid material was filtered off and washed with Ac_2O. Removal of the solvent left a brown residue which was chromatographed on silica gel. Elution with 10% MeOH in $CHCl_3$ provided bright crystals crystal of **17**, m.p. 219.5–220° (dec) ($CHCl_3$). PMR δ 2.58 (3H, s, CH_3CO), 3.80 (3H, s, N–CH_3), 4.94 (2H, s, CH_2), 6.93 (1H, t, J = 7 Hz, H3), 7.53 (1H, d, J = 7 Hz, H4), 7.82 (1H, d, J = 7 Hz, H2). (Found: C, 64.47; H, 5.50; N, 6.84. Calc. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83%).

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