

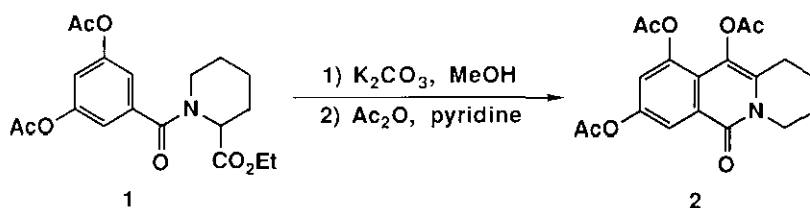
# BASE-INDUCED CONDENSATION OF PHENOLS JOINED BY AMIDES TO KETONES: A SYNTHESIS OF HYDROXYLATED ISOQUINOLINONES AND DERIVATIVES

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**Abstract**—Potassium carbonate in methanol saponified the acetate ester groups of certain *meta*-acetoxylated  $\alpha$ -benzamido ketones and cyclized the resulting phenols *in situ* to give a series of hydroxylated isoquinolinones and derivatives.

Saponification of  $\alpha$ -benzamido ester **1** gave a somewhat unexpected result, encountered in the course of other work.<sup>1</sup> Cyclization occurred, forming a carbon-carbon bond and yielding a tricyclic isoquinolinone derivative, characterized as **2** after re-esterification. Similarly, the analogous  $\alpha$ -benzamido ketone **3.6**<sup>2</sup> (Table) also formed a 2-pyridone ring, and the product (**4.6**) inhibited 5-lipoxygenation of arachidonic acid *in vitro*.<sup>3</sup> Prompted by this latter finding, we extended the series hoping to find the best member. Here we report our chemical results (Table). They comprise a novel,<sup>4</sup> intramolecular, base-induced condensation (**3.0**  $\rightarrow$  **4.0**) of phenols joined by amides to ketones. The condensation provided hydroxylated isoquinolinones (**4.1**–**4.3**) as well as linearly and angularly fused tricyclic isoquinolinone derivatives (**4.4**–**4.11**). Rings fused to the isoquinolinone skeleton were 5- or 6-membered.



$\alpha$ -Benzamido ketones (**3.0**) bearing *meta*-substituted acetoxy groups served as starting materials. The *meta*-substituents were chosen in the expectation that phenolates (e.g., [5]) mediated condensation, as do enolates in aldol reactions. Analogous to aldols, three tertiary carbinols (**6**–**8**) were isolated, and two proved to be intermediates. Carbinols **6** and **8** both eliminated the elements of water during esterification, yielding the aromatic **4.7** and **4.5**, respectively. A by-product related to isoquinolinone derivative **4.10** was exocyclic olefin **9**.

The condensation products **4.8** and **4.10**,<sup>5</sup> which respectively comprised unsymmetrical 3,4- and 3-substituted benzoic acid units, might have been obtained as mixtures of positional isomers, but were not. We isolated only **4.8** and **4.10**, but cannot exclude the chance that any isomers went unnoticed despite monitoring by tlc.

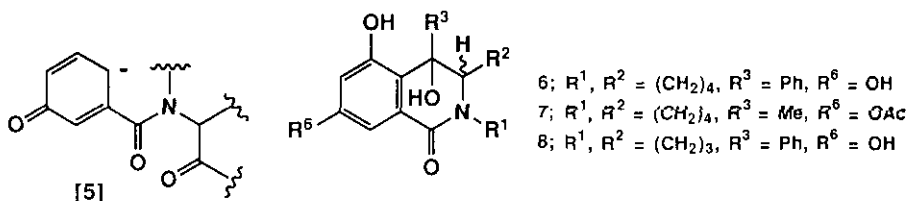
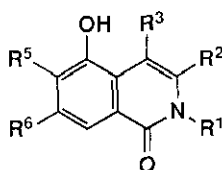
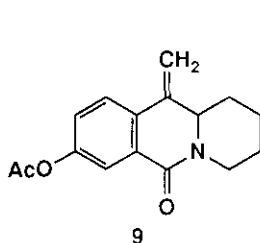


Table. Cyclizations of Amide Ketones (3.0) to Isoquinolinone Derivatives (4.0)

| R <sup>1</sup>                     | R <sup>2</sup>                     | R <sup>3</sup> | R <sup>4</sup> | R <sup>5</sup> | R <sup>6</sup> | R <sup>7</sup> | Yields (%) of 4.0 <sup>a</sup> | mp (°C) <sup>b</sup> of 4.0 |
|------------------------------------|------------------------------------|----------------|----------------|----------------|----------------|----------------|--------------------------------|-----------------------------|
| H                                  | H                                  | Me             | AcO            | H              | AcO            | H              | 4.1, 41                        | 226-228                     |
| H                                  | H                                  | Ph             | AcO            | H              | AcO            | H              | 4.2, 100                       | 248-251                     |
| H                                  | Me                                 | Ph             | AcO            | H              | AcO            | H              | 4.3, 72                        | 294-296                     |
| —(CH <sub>2</sub> ) <sub>3</sub> — |                                    | Me             | AcO            | H              | AcO            | H              | 4.4, 61                        | 180-182                     |
| —(CH <sub>2</sub> ) <sub>3</sub> — |                                    | Ph             | AcO            | H              | AcO            | H              | 4.5, 18                        | 184-185                     |
| —(CH <sub>2</sub> ) <sub>4</sub> — |                                    | Me             | AcO            | H              | AcO            | H              | 4.6, 54                        | 174-176                     |
| —(CH <sub>2</sub> ) <sub>4</sub> — |                                    | Ph             | AcO            | H              | AcO            | H              | 4.7, 62                        | 179-182                     |
| —(CH <sub>2</sub> ) <sub>4</sub> — |                                    | Me             | AcO            | AcO            | H              | H              | 4.8, 21                        | 186-188                     |
| —(CH <sub>2</sub> ) <sub>4</sub> — |                                    | Me             | H              | H              | AcO            | AcO            | 4.9, 59                        | 181-182                     |
| —(CH <sub>2</sub> ) <sub>4</sub> — |                                    | Me             | H              | H              | AcO            | H              | 4.10, 22                       | 116-118                     |
| H                                  | —(CH <sub>2</sub> ) <sub>4</sub> — |                | AcO            | H              | AcO            | H              | 4.11, 43                       | 257-260                     |

<sup>a</sup> Characterized by microanalysis ( $\pm 0.4\%$  for C, H, and N) and by ir, <sup>1</sup>H-nmr, and mass spectra. <sup>b</sup> Uncorrected.



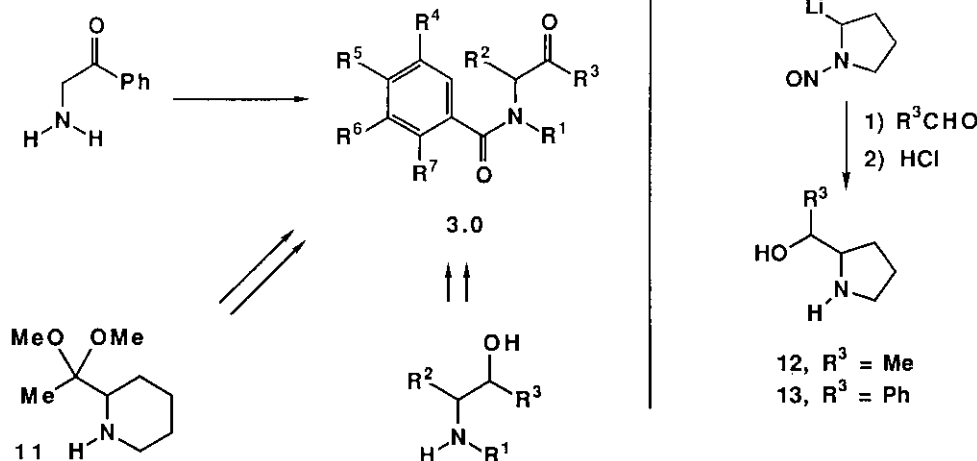
10.1; R<sup>1</sup> = R<sup>2</sup> = H, R<sup>3</sup> = Ph, R<sup>5</sup> = H, R<sup>6</sup> = OH

10.2; R<sup>1</sup> and R<sup>2</sup> = (CH<sub>2</sub>)<sub>4</sub>, R<sup>3</sup> = Me, R<sup>5</sup> = OH, R<sup>6</sup> = H

10.3; R<sup>1</sup> = H, R<sup>2</sup> and R<sup>3</sup> = (CH<sub>2</sub>)<sub>4</sub>, R<sup>5</sup> = H, R<sup>6</sup> = OH

Ester hydrolyses accompanied cyclizations of 3.0, directly yielding phenols, *e.g.* 10.1-10.3. In general, re-esterification of the phenols to acetates 4.0 facilitated purification and characterization. Phenols 10.1-10.3 in addition to 6 and 8 could be readily purified without esterification, however.

One or more of three methods furnished  $\alpha$ -benzamido ketones 3.0: direct benzoylation<sup>6</sup> of  $\alpha$ -aminoacetophenone, benzoylation of  $\alpha$ -amino ketal 11<sup>1a</sup> followed by hydrolysis of the ketal, or N-benzoylation of  $\alpha$ -amino alcohols followed by oxidation of the alcohol (Scheme). In all three methods, benzoyl chlorides served to amidate the amines.  $\alpha$ -Benzamido ketone 3.2 resulted from direct benzoylation, 3.6 and 3.8-3.10 from benzoylation and hydrolysis, and ketones 3.1, 3.3-3.5, 3.7, and 3.11 came from benzoylation of  $\alpha$ -amino alcohols. Jones' reagent<sup>7</sup> or pyridinium chlorochromate<sup>8</sup> converted the resulting  $\alpha$ -amido alcohols to the starting  $\alpha$ -benzamido ketones.



To make  $\alpha$ -benzamido ketones **3.4** and **3.5** required  $\alpha$ -amino alcohol **12**, known only as a halomycin degradation product,<sup>9</sup> as well as the previously unknown **13**.<sup>10</sup> Additions of 2-lithio-1-nitrosopyrrolidine to acetaldehyde and benzaldehyde furnished both compounds **12** and **13**, according to a standard method.<sup>11</sup>

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<sup>1</sup> (a) R. Brambilla, R. Friary, A. Ganguly, M. S. Puar, B. R. Sunday, J. J. Wright, K. D. Onan, and A. T. Mc Phail, *Tetrahedron*, 1981, **37**, 3615; (b) R. Brambilla, R. Friary, A. Ganguly, M. S. Puar, J. G. Topliss, R. Watkins, and A. T. Mc Phail, *J. Org. Chem.*, 1982, **47**, 4137.

<sup>2</sup> Substituents of the amide ketones **3.1-3.11** correspond to those tabulated for isoquinolinone derivatives (**4.1-4.11**, respectively).

<sup>3</sup> R. Friary, U. S. Patent Application No. 208,304 (July 17, 1988).

<sup>4</sup> An intramolecular condensation of 3-hydroxy- or 3-methoxybenzoates of hydroxyacetone offers the closest precedent. This condensation, which occurs under strongly acidic conditions (90%  $\text{H}_2\text{SO}_4$ ), converts these esters to isochromanones: H. K. Desai and R. N. Usgaonkar, *J. Indian Chem. Soc.*, 1964, **41**, 821 (*Chem. Abstr.* 1965, 62,16179e).

<sup>5</sup> A typical procedure for converting **3.0** to **4.0** follows.

A mixture of amide ketone **3.6** (27.9 g, 0.080 mol), potassium carbonate (22.2 g), and methanol (270 ml) was stirred for 23 h at 25°C under a nitrogen atmosphere. The mixture was poured onto ice (1.5 kg) and 1 N hydrochloric acid (360 ml). The precipitate was collected by filtration, dried, and crystallized from ethanol to give 1,2,3,4-tetrahydro-8,10-dihydroxy-11-methyl-6H-benzo[b]quinolizin-6-one (14.2 g, 71.8%), mp 319-321°C, as an orange powder; ir:  $\nu_{\text{max}}$  (mineral oil) 3290, 3110, 1620  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  ( $\text{DMSO}-d_6$ , 80 MHz):  $\delta$  1.53-1.89 (m, 4H,  $H(2)$  and  $H(3)$ ), 2.44 (s, 2H,  $\text{CH}_3$ ), 2.72 (t,  $J(1-2) = 7$  Hz, 2H,  $H(1)$ ), 3.92 (t,  $J(4-3) = 7$ , 2H,  $H(4)$ ), 6.61 (d,  $J(9-7) = 3$ , 1H,  $H(9)$ ), 7.14 (d,  $J(7-9) = 3$ , 1H,  $H(7)$ ), 9.48 (s, 1H, OH, ex.), 9.76 (s, 1H, OH, ex.) ppm; uv:  $\lambda_{\text{max}}$  (MeOH) 378 ( $\epsilon = 3.74$ ), 361 (3.85), 348 (3.72), 299 (4.02), 289 (4.05), 244 (4.40) nm; EI-*ms*:  $m/z$  246 (30%,  $[\text{M} + 1]^+$ ), 245 (100,  $\text{M}^+$ ), 244 (48,  $[\text{M} - 1]^+$ ), 230 (55,  $[\text{M} - \text{Me}]^+$ ). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{15}\text{NO}_3$ : C, 68.55; H, 6.16; N, 5.71. Found: C, 68.53; H, 6.19; N, 5.52.

Acetic anhydride (12 ml) and pyridine (12 ml) in chloroform (240 ml) at reflux for 18 h esterified 1,2,3,4-tetrahydro-8,10-dihydroxy-11-methyl-6H-benzo[b]quinolizin-6-one (7.26 g). Standard workup gave 8,10-bis(acetyloxy)-1,2,3,4-tetrahydro-11-methyl-6H-benzo[b]quinolizin-6-one (**4.6**) (5.30 g, 46.6%);  $\nu_{\text{max}}$  1760 (CO), 1640 (CO)  $\text{cm}^{-1}$ ;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ , 80 MHz):  $\delta$  1.71-2.01 (m, 4H,  $H(2)$  and  $H(3)$ ), 2.29 and 2.33 (s and s,

9H, 2  $\text{CH}_3\text{CO}$  and  $\text{CH}_3$ ), 2.80 (t,  $J$  (1-2) = 7, 2H,  $H(1)$ ), 4.11 (t,  $J$  (4-3) = 7, 2H,  $H(4)$ ), 7.12 (d,  $J$  (9-7) = 3, 1H,  $H(9)$ ), 8.13 (d,  $J$  (7-9) = 3, 1H,  $H(7)$ ) ppm; uv:  $\lambda_{\text{max}}$  (MeOH) 350 (3.74), 298 (4.07) nm; EI-*ms*:  $m/z$  329 (12,  $\text{M}^+$ ), 287 (22,  $[\text{M} - \text{C}_2\text{H}_2\text{O}]^+$ ), 245 (100,  $[\text{M} - 2\text{C}_2\text{H}_2\text{O}]^+$ ). *Anal.* Calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}_5$ : C, 65.64; H, 5.81; N, 4.25. Found: C, 65.72; H, 5.80; N, 4.47.

<sup>6</sup> A typical procedure for carrying out benzoylation and hydrolysis follows.

A mixture of 3,5-diacetoxybenzoyl chloride (25.7 g, 0.100 mol), 2-(1,1-dimethoxyethyl)piperidine hydrochloride<sup>1a</sup> (21.1 g, 0.100 mol), and diisopropylethylamine (28 g, 0.22 mol) in dichloromethane (400 ml) was stirred for 1.75 h at 0-5 °C and overnight at 25 °C. The solution was washed with water, 1M sodium bicarbonate solution, and with brine. The dried (sodium carbonate), filtered solution was concentrated to give the amide acetal (42.9 g) as a brown oil.

A solution of crude amide acetal (42.5 g) in ether (150 ml) was added to 1N hydrochloric acid (100 ml) at 0-5 °C, and the resulting mixture was stirred for 1 h. The layers were separated, and the aqueous layer was extracted with ether. Combined organic layers were washed with 1M sodium bicarbonate and with water, and were dried (sodium carbonate), filtered and concentrated to give 2-acetyl-1-[3,5-bis(acetyloxy)benzoyl]-piperidine (3.6) (28.3 g, 81%) as a yellow oil; ir:  $\nu_{\text{max}}$  1780 (CO), 1730 (CO), 1640 (CO)  $\text{cm}^{-1}$ ; <sup>1</sup>H-nmr ( $\text{CDCl}_3$ , 80 MHz):  $\delta$  1.35-1.85 (br m, 5H,  $H(3)$ ,  $H(4)$ , and  $H(5)$ ), 2.18 and 2.26 (s and m, 11 H, 2  $\text{CH}_3\text{COO}$ ,  $\text{CH}_3\text{C(=O)C}$ ,  $H(6)$ ), 5.14-5.40 (m, 1H,  $H(2)$ ), 6.90-7.17 (m, 3H, Ar) ppm; EI-*ms*:  $m/z$  305 (13,  $[\text{M} - \text{C}_2\text{H}_2\text{O}]^+$ ), 304 (73,  $[\text{M} - \text{C}_2\text{H}_3\text{O}]^+$ ), 263 (2,  $[\text{M} - 2\text{C}_2\text{H}_3\text{O}]^+$ ), 221 (100,  $[\text{3,5-(AcO)}_2\text{C}_6\text{H}_3\text{C=O}]^+$ ), 179 (96,  $[\text{3,5-C}_6\text{H}_3(\text{OH})(\text{OAc})\text{C=O}]^+$ ), 137 (84,  $[\text{3,5-(HO)}_2\text{C}_6\text{H}_3\text{C=O}]^+$ ).

<sup>7</sup> A. Bowers, T. G. Halsall, E. H. R. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.

<sup>8</sup> E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.

<sup>9</sup> A. K. Ganguly, S. Szmulewicz, O. Z. Sarre, D. Greeves, J. Morton, and J. Mc Glotten, *Chem. Commun.*, 1974, 395.

<sup>10</sup> Other starting materials were items of commerce or known compounds.

<sup>11</sup> (a) D. Seebach, D. Enders, and B. Renger, *Chem. Ber.*, 1977, 110, 1852; (b) D. Seebach and D. Enders *Chem. Ber.*, 1975, 108, 1293.

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