

**SYNTHESIS OF 4,6-DIHYDRO-4-OXOPYRIDO[2,1-*a*]ISOINDOLES AND  
4,6-DIHYDRO-6-OXOTHIENO[2',3':3,4]PYRROLO[1,2-*a*]PYRIDINES**

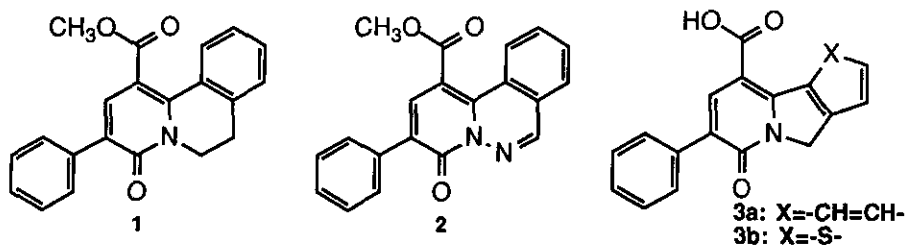
Serge Burner, Rolf Canesso, and Ulrich Widmer\*

Pharma Division, Preclinical Research  
F. Hoffmann-La Roche Ltd.  
CH-4002 Basel, Switzerland

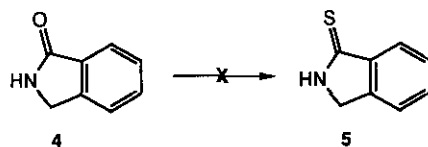
**Abstract** - Tricyclic pyridones (3) which are important intermediates for the preparation of potent benzodiazepine receptor ligands were obtained by different chemical routes. Key reaction in the so far optimal synthesis of 3a is the base catalyzed ring contraction reaction of 2 to intermediate (13). Under similar reaction conditions, however, thiophene derivative (14) yielded instead of the analogous acid (16), the nitrile (15). In two additional steps the final product (3b) was obtained in good yield.

Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

We recently described the synthesis of a series of tricyclic pyridone derivatives that showed a high affinity for the benzodiazepine receptor complex, *e.g.* 4-oxo-4*H*-benzo[*a*]quinolizine (1)<sup>1</sup> and 4-oxo-4*H*-pyrido[2,1-*a*]phthalazine (2).<sup>2</sup>

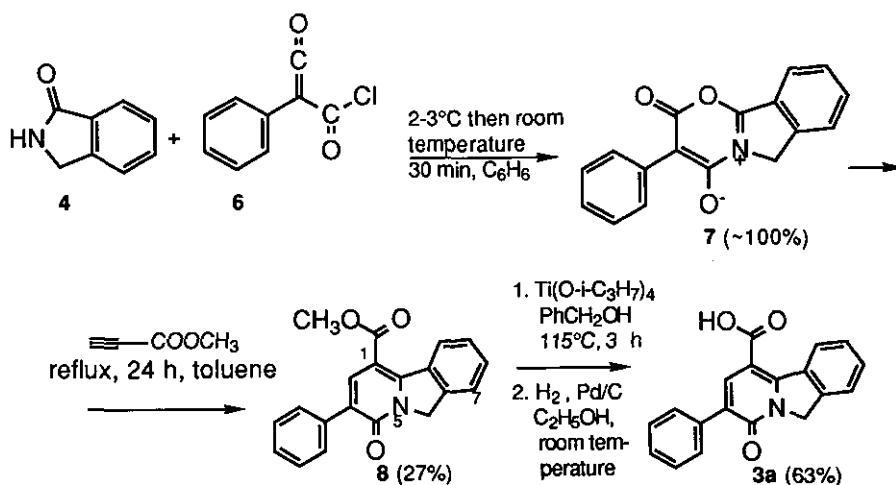


We now report on the synthesis of the analogs (3a) and (3b)<sup>3</sup> that are intermediates used for the preparation of corresponding amides.<sup>4</sup> First, we applied the previous route,<sup>1</sup> however, this approach failed because the desired thiolactam (5) could not be isolated after reacting 4 with various thiolation reagents (Scheme 1).



Scheme 1

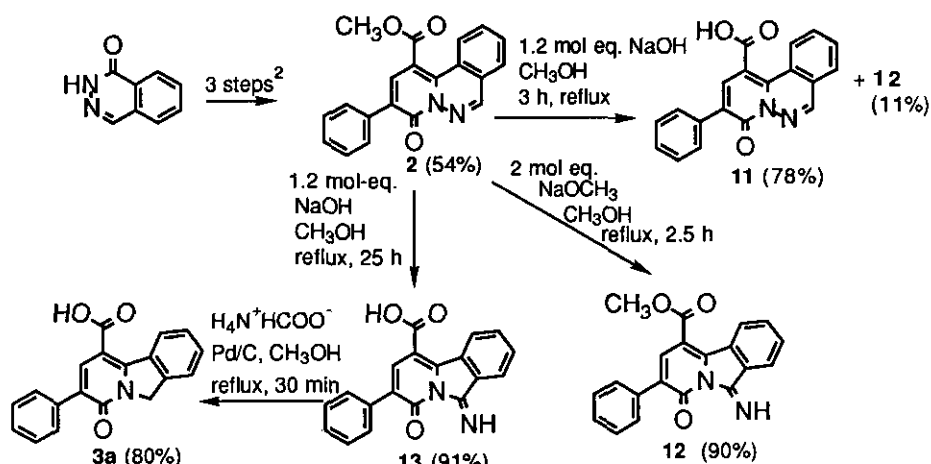
Pyridone (3a) could be obtained by a modified procedure that avoided the preparation of 5 (Scheme 2).



Scheme 2

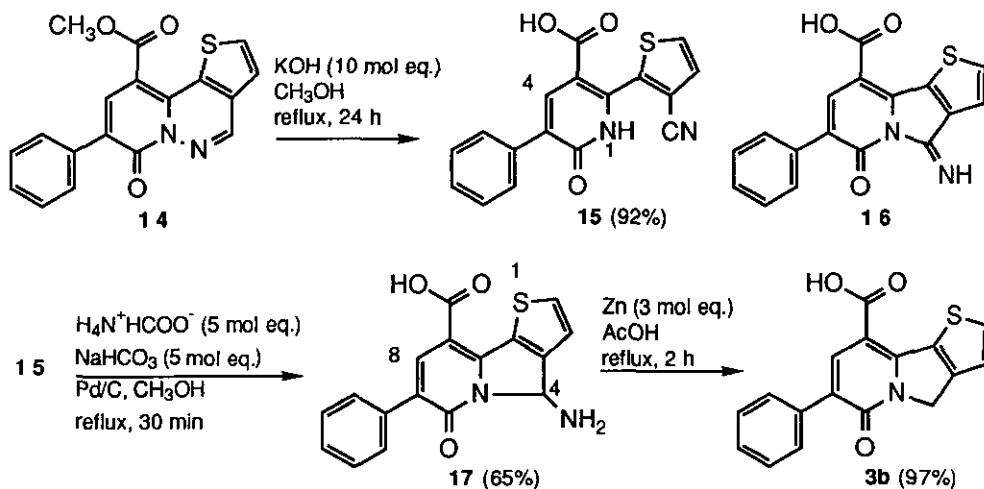
The novel mesoionic oxazine derivative (7) (cf. 5) was prepared in quantitative yield by reaction of isoindolone (4) with the ketene (6).<sup>6</sup> 1,4-Dipolar cycloaddition of 7 with methyl propiolate led, after extrusion of CO<sub>2</sub> under the reaction conditions, in regioselective manner but in an unsatisfactory yield to the ester (8).<sup>5,7</sup> The preparation of the acid (3a)<sup>8</sup> could only be achieved by transesterification<sup>9</sup> with benzyl alcohol and subsequent hydrogenolysis.<sup>10</sup>

The low yield in the transformation of 7 to 8 prompted us to look for an alternative preparation of the acid (3a). Fortunately, we found that upon saponification of the ester (2) besides the expected acid (11) a by-product (12) was formed in 11% yield (Scheme 3).<sup>11</sup> Upon heating of 2 with sodium methoxide, 12 was obtained as the only product in 90% yield.



Scheme 3

The prolonged reaction of **2** with sodium hydroxide furnished the acid (**13**),<sup>12</sup> which was hydrogenolyzed providing in high yield the target molecule (**3a**). This methodology was also applied to thiophene derivative (**14**) (Scheme 4).



Scheme 4

Unexpectedly, in this case the nitrile derivative (**15**)<sup>13</sup> and not **16**, as in the case of the benzo-analog (**2**), was formed exclusively in high yield. Under carefully controlled reductive

conditions, cyclisation was achieved providing 17.<sup>14</sup> The preparation of the acid (3b)<sup>15</sup> was completed by reductive removal of the amino group with zinc in acetic acid.

From a mechanistic viewpoint, the transformation of 14 to 15 formally represents an intramolecular variant of the nitrile synthesis published by A. R. Katritzky *et al.* in 1976,<sup>16</sup> a transformation which could also be effected with NaNH<sub>2</sub> as a base.<sup>17</sup>

In conclusion, the application of this synthetic methodology to our substrates made possible the straightforward preparation of the target molecules (3a) and (3b), respectively.

#### ACKNOWLEDGEMENT

We thank our colleagues from the spectroscopic department for EI-ms (Mr. W. Meister, Dr. W. Vetter), ir- (Mr. A. Bubendorf) and nmr-spectra (Drs. W. Arnold, G. Englert). Furthermore, we thank Dr. L. F. Courtney for proof-reading the manuscript.

#### REFERENCES AND NOTES

1. U. Fischer, H. Möhler, F. Schneider, and U. Widmer, *Helv. Chim. Acta*, 1990, **73**, 763.
2. U. Fischer, F. Schneider, and U. Widmer, *Eur. Pat.* 226'196, June 24, 1987 (*Chem. Abstr.*, 1987, **107**, 198'348 p).
3. S. Burner and U. Widmer, *Eur. Pat.* 472'166, Febr. 26, 1992 (*Chem. Abstr.*, 1992, **116**, 235'450z).
4. Actually, the pharmacologically relevant derivatives are the amides. Synthesis and pharmacological characterization of these compounds will be published in due course.
5. a) W. Friedrichsen, E. Kujath, G. Liebezeit, R. Schmidt, and I. Schwarz, *Liebigs Ann. Chem.*, 1978, 1655. b) W. Friedrichsen, C. Krüger, E. Kujath, G. Liebezeit, and S. Mohr, *Tetrahedron Lett.*, 1979, 237. c) W. Friedrichsen, R. Schmidt, G.J. van Hummel, and D.M.W. van den Ham, *Liebigs Ann. Chem.*, 1981, 521. d) K. T. Potts, M. O. Dery, and R. K. Kullnig, *J. Chem. Soc., Chem. Commun.*, 1987, 840.
6. E. Ziegler and H. Sterk, *Monatsh. Chem.*, 1967, **98**, 1104.
7. Spectral data of 8: Ir (KBr)  $\nu_{\max}$  1720, 1630, 1537, 1247 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>, 250 MHz)  $\delta$  3.98 (3H, s, OCH<sub>3</sub>), 5.21 (2H, s, CH<sub>2</sub>), 7.20 - 7.75 (6H, m, arom. H), 7.80 - 7.85 (2H, m, arom. H), 8.31 (1H, s, H-C(2)), 9.02 (1H, d, J = 7.5 Hz, H-C(10)). EI-ms m/z (%): 317 (M<sup>+</sup>, 100), 286 (12), 258 (11), 230 (17); mp 206 - 207°C (Ethyl acetate).
8. Spectral data of 3a: Ir (KBr)  $\nu_{\max}$  3050, 1710, 1616, 1539, 1212 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>, 250 MHz)  $\delta$  5.22 (2H, s, CH<sub>2</sub>), 7.31 - 7.52 (3H, m, arom. H), 7.50 - 7.75 (2H, m, arom. H), 7.85 - 7.95 (3H, m, arom. H), 8.25 (1H, s, H-C(2)), 8.95 (1H, d, J = 7.5 Hz, H-C(10)), 13.40 (1H, br s, COOH).

- El-ms m/z (%): 303 (M<sup>+</sup>, 100), 259 (8), 258 (12), 230 (24); mp 298 - 300°C (decomp., CH<sub>3</sub>CN/DMF 5:2).
9. D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidmann, and M. Züger *Synthesis*, **1982**, 138.
10. Usual saponification procedures led to decomposition of the starting material.
11. Spectral data of **12**: Ir (KBr)  $\nu_{\max}$  3249, 1725, 1688, 1641, 1599, 1286 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>, 250 MHz)  $\delta$  4.00 (3H, s, OCH<sub>3</sub>), 7.38 - 7.51 (3H, m, arom. H), 7.61 - 7.75 (4H, m, arom. H), 8.06 (1H, s, H-C(2)), 8.15 - 8.25 (1H, m, arom. H), 8.71 - 8.82 (1H, m, arom. H), 11.88 (1H, br s, NH). El-ms m/z (%) 330 (M<sup>+</sup>, 100), 299 (12), 297 (18), 271 (42), 242 (14); mp 170 - 171°C (CH<sub>3</sub>CN).
12. Spectral data of **13**: Ir (KBr)  $\nu_{\max}$  3222, 1683, 1644s, 1600, 1240 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>, 250 MHz)  $\delta$  7.30 - 7.56 (3H, m, arom. H), 7.62 - 7.88 (4H, m, arom. H), 7.96 - 8.10 (1H, m, arom. H), 8.03 (1H, s, H-C(2)), 8.74 (1H, d, J = 7.0 Hz, H-C(10)), 11.72 (1H, br s, NH), 14.0 (1H, br s, COOH). El-ms m/z (%) 316 (M<sup>+</sup>, 100), 271 (52), 242 (16); mp 274 - 275°C (decomp., CH<sub>3</sub>OH/DMF 1:1).
13. Spectral data of **15**: Ir (KBr)  $\nu_{\max}$  3467, 2234, 1680, 1635, 1599, 1249, 1215 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  7.38 - 7.45 (3H, m, arom. H, C<sub>6</sub>H<sub>5</sub>), 7.56 (1H, d, J = 5.0 Hz, thioph.H), 7.57 (1H, s, H-C(4)), 7.75 - 7.79 (2H, m, arom. H, C<sub>6</sub>H<sub>5</sub>), 7.97 (1H, d, J = 5.0 Hz, thioph. H), 8.08 (1H, br s, NH), 12.80 (1H, br s, COOH). El-ms m/z (%) 322 (M<sup>+</sup>, 100), 303 (12), 277 (64), 250 (10); mp 255 - 257°C (decomp., CH<sub>3</sub>OH).
14. Spectral data of **17**: Ir (KBr)  $\nu_{\max}$  1684, 1634, 1599, 1549, 1393, 1264 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>, 90 MHz),  $\delta$  6.18 (1H, s, H-C(4)), 7.29 (1H, d, J = 5.0 Hz, H-C(2)), 7.20 - 7.55 (3H, m, arom. H), 7.55 - 8.05 (3H, m, arom. H), 8.15 (1H, s, H-C(8)). El-ms m/z (%) 324 (M<sup>+</sup>, 16), 322 (100), 279 (50), 277 (78), 250 (20), 236 (26); mp 238 - 243°C (decomp., CH<sub>3</sub>OH).
15. Spectral data of **3b**: Ir (KBr)  $\nu_{\max}$  1690, 1634, 1603, 1546, 1415, 1286 cm<sup>-1</sup>. <sup>1</sup>H-Nmr (DMSO-d<sub>6</sub>, 250 MHz)  $\delta$  5.06 (2H, s, H-C(4)), 7.25 - 7.60 (4H, m, arom. H), 7.70 - 7.86 (2H, m, arom. H), 7.90 - 8.04 (1H, m, arom. H), 8.24 (1H, s, H-C(8)). El-ms m/z (%) 309 (M<sup>+</sup>, 100), 264 (20), 236 (32); mp > 300°C (DMF).
16. J. B. Bapat, R. J. Blade, A. J. Boulton, J. Epsztajn, A. R. Katritzky, J. Lewis, P. Molina-Buendia, P.-L. Nie, and C. A. Ramsden, *Tetrahedron Lett.*, **1976**, 2691.
17. M. Alajarin, P. M. Fresneda, P. Molina, and A. Soler, *An. Quim.*, **1979**, **75**, 124 (*Chem. Abstr.*, **1979**, **91**, 74423r).