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Mechanism of an unusual decarboxylative cyclization

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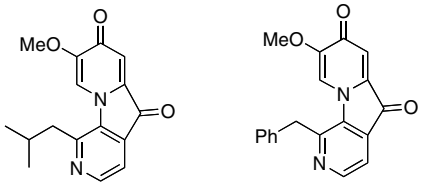
Abstract—The mechanism of an unusual decarboxylative cyclization from 5-methoxy-1-(2-carboxyphenyl)-1,4-dihydro-4-oxopyridine-2-carboxylic acid (diacid) to 3-methoxypyrido[1,2-*a*]indole-2,10-dione (ketone) has been investigated. ^{13}C-labeling has demonstrated that the carbonyl carbon of the ketone arises exclusively from the anthranilic acid carboxyl of the diacid. A zwitterionic mechanism has been proposed.

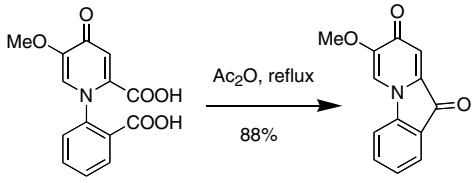
Pterocellins A (**1**) and B (**2**) are antineoplastic alkaloids (Fig. 1) recently isolated from a New Zealand marine Bryozoan.[1] NMR studies on these substances, supported by a single crystal X-ray structure determination on the deep red Pterocellin A, reveal that these compounds possess the structurally novel pyrido[4,3-*b*]indolizine-5,7-dione core, a deceptively simple yet challenging synthetic target.

In surveying potential routes to the Pterocellins we discovered that the benzenoid counterpart of their core, namely 3-methoxypyrido[1,2-*a*]indole-2,10-dione (**4**) had been described in 1997 by Korenova et al.[2] In that report, the model core **4** had been produced in high yield as a dark red solid, mp 204–206 °C, by heating 5-methoxy-1-(2-carboxyphenyl)-1,4-dihydro-4-oxopyridine-2-carboxylic acid (**3**) in refluxing acetic anhydride (Scheme 1).



1 : PTEROCELLIN A **2** : PTEROCELLIN B

Figure 1.



3 **4**

Scheme 1.

Since the relatively mild decarboxylative cyclization of diacid **3** to ketone **4** was unusual, we undertook to confirm Korenova's observations. In fact, when diacid **3** is held at 100 °C in acetic anhydride for several hours (optimum conditions), a dark red crystalline ketone melting at 251–252 °C was obtained in nearly quantitative yield. Despite the melting point discrepancy, the ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS of our product were in agreement with the data of Korenova, and in full accord with the proposed tricyclic structure **4**.[3] With the Korenova cyclization thus confirmed, we considered that this unusual ring closure may represent an intramolecular acylation of the pendant anthranilic acid ring by an activated pyridone-2-carboxyl group (Scheme 2).

Two new experimental observations cast doubt on the above mechanism. When 5-methoxy-1-phenyl-1,4-dihydro-4-oxopyridine-2-carboxylic acid (**7**) was heated in acetic anhydride or in dimethyl sulfoxide, no cyclization was observed, and only the decarboxylation product **8** was isolated. In contrast, pyridone ester **9** in DMSO at 120 °C was smoothly converted to the tricyclic ketone **4** in 91% yield (Scheme 3).

Keywords: Mechanism; Decarboxylative cyclization.
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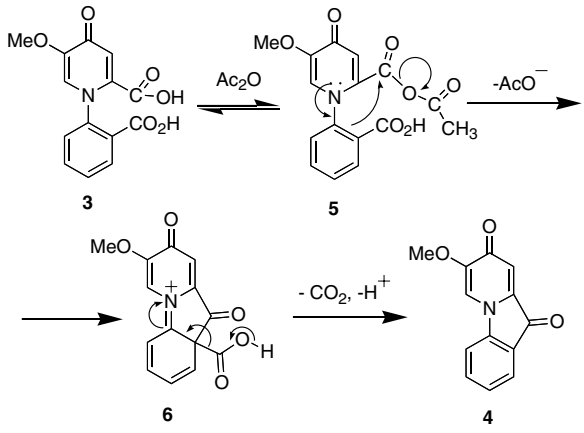
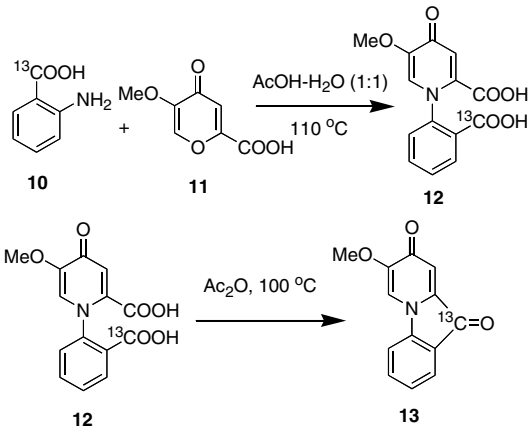
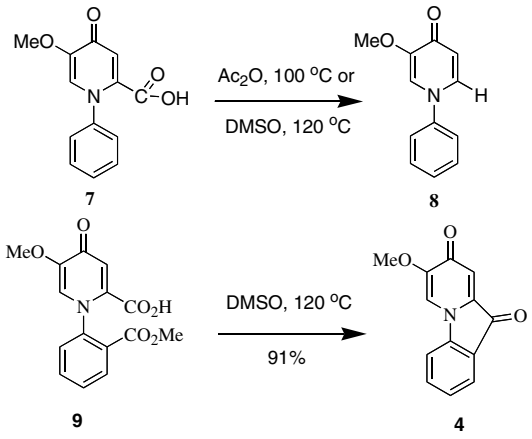


Scheme 2.



Scheme 4.

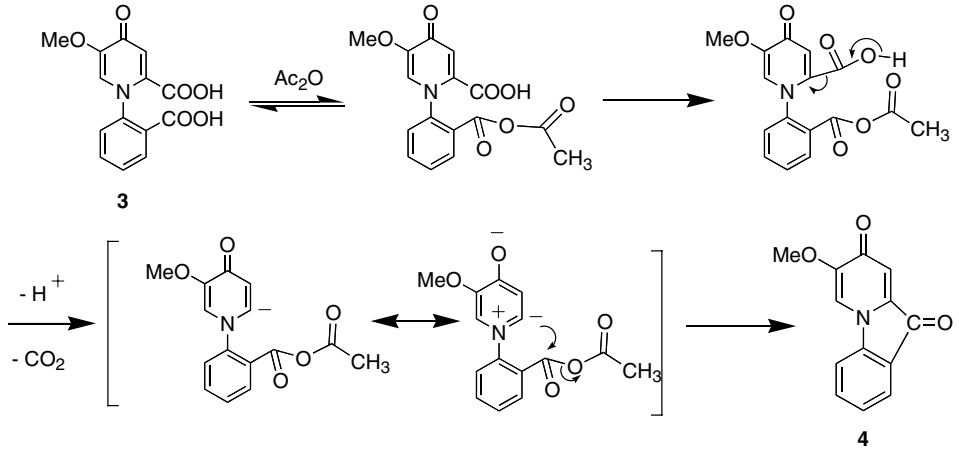


Scheme 3.

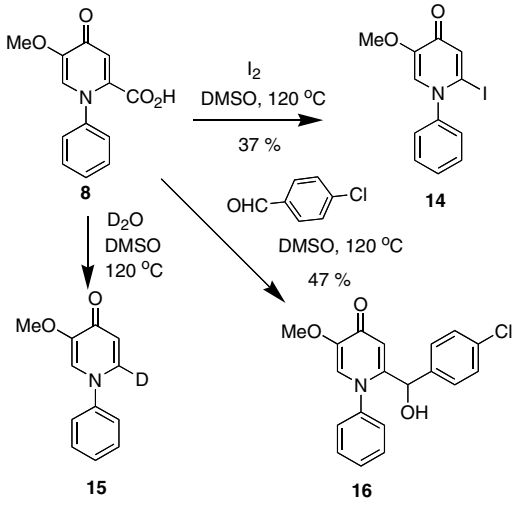
In order to firmly establish the origin of the ketone carbonyl in product **4**, a ^{13}C-labeled precursor **12** was synthesized by condensation of ^{13}C-anthranilic acid **10** (prepared in three steps from 2-bromonitrobenzene and Cu^{13}CN)[4] with the methoxypyranone acid **11** as shown in Scheme 4. When this ^{13}C-labeled **12** was heated in acetic anhydride at 100 °C for several hours, the red crystalline ketone product **13** was identified as having retained all of the original ^{13}C-label at the new carbonyl group. Thus, ketone **13** showed in the ^{13}C NMR a huge peak at 183.8 ppm for the ^{13}C-carbonyl carbon, and in the mass spectrum the $[MH]^+$ ion was at $m/z = 229$, with the $m/z = 228$ peak for the unlabeled compound **4** absent. Moreover, in the ^{1}H NMR, long-range coupling of the ^{13}C-carbonyl carbon to both adjacent *ortho* protons could be clearly seen, with $J = 2.8$ Hz.[5] The above data establish that the ketone carbonyl in the cyclization of **3** arises from the anthranilic carboxyl, and not from the pyridone carboxyl.

The preceding results led to a new mechanism (Scheme 5) in which the C(2) pyridone carbon loses H^+ and CO_2 to become an anionic nucleophilic center, which subsequently attacks the anthranilic carboxyl. There is some literature analogy for direct C(2) anion formation from *N*-alkyl-4-oxo-pyridines using *n*-BuLi at −78 °C,[6] and from deuterium exchange at 100 °C.[7]

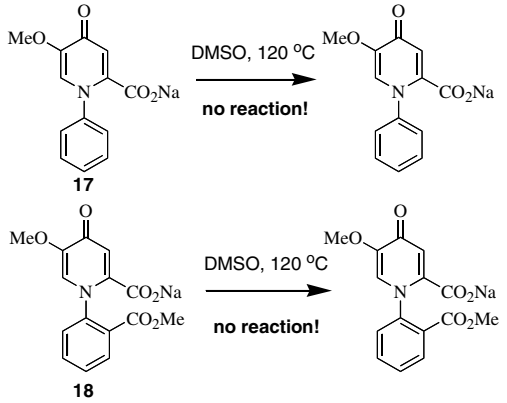
We obtained evidence consistent with C(2) nucleophilicity by heating pyridone acid **7** in DMSO at 120 °C in the presence of weak electrophiles, leading to **14**,[8] **15**,[9] and **16**,[10] as summarized in Scheme 6.



Scheme 5.



Scheme 6.



Scheme 7.

Two subsequent experiments employing the sodium salt of acid **7** and ester acid **9** required us to further revise the second mechanism (Scheme 5). We found that no decarboxylation occurred upon heating the salt **17** in DMSO at 120 °C for many hours. Moreover, the sodium salt **18** was similarly stable under these conditions (Scheme 7).

These last results led us to a third mechanism (Scheme 8) which requires the participation of the carboxyl proton to drive a zwitterionic reaction sequence.

This last mechanism appears to fit all of our data and is entirely consistent with the 1965 observation of Beak and Bonham[7] on the rapid decarboxylation of 4-methoxypyridinium-2-carboxylates, as well as with the early work of Hammick and co-workers[11] on the decarboxylation of α-picolinic acid. To our knowledge this is the first example of the use of such decarboxylations to form fused pyridone ring systems.

References and notes

1. Yao, B.; Prinsep, M. K.; Gordon, D. P. *J. Nat. Prod.* **2003**, *66*, 1074–1077.
2. Korenova, A.; Povazanec, F.; Uher, M.; Hajas, M. *Chem. Papers* **1997**, *51*, 383–389.
3. Compound **4**: Mp: 251–252 °C. MS (API-ES, positive): *m/z* 228.2 $[MH]^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, J = 7.5 Hz, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.46 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.03 (s, 1H), 3.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 183.8, 174.1, 169.1, 151.7, 147.4, 136.9, 126.0 (2C), 123.1, 113.3, 111.7, 110.0, 56.7. HRMS (DCI): calcd for $C_{13}H_{10}NO_3$ $[MH]^+$ *m/z* 228.0661, found 228.0660.
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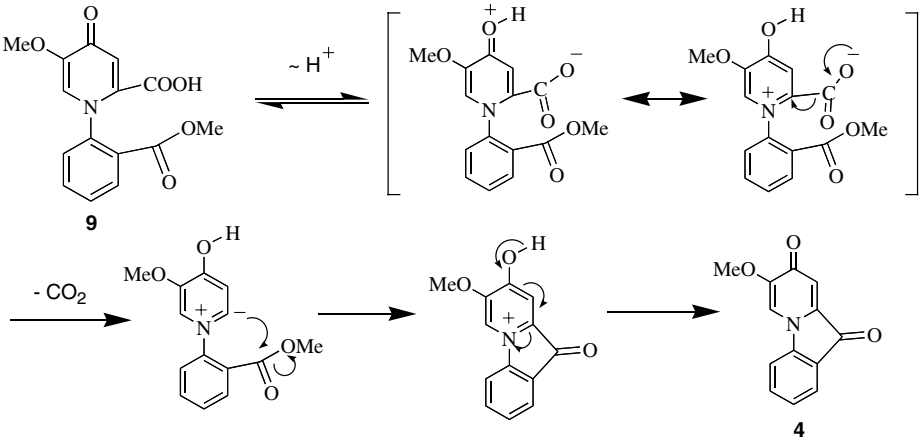
5. Compound **13**: Mp: 251–252 °C. MS (API-ES, positive): *m/z* 229.1 $[MH]^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (dd, J = 7.3, 2.8 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.50 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 3.93 (s, 3H). HRMS (DCI): calcd for $C_{12}{}^{13}CH_{10}NO_3$ $[MH]^+$ *m/z* 229.0694, found 229.0699. The observed $^3J_{C-H}$ of 2.8 Hz is similar to the 4.08 Hz coupling constant found for analogous *ortho* $^3J_{C-H}$ coupling in ^{13}C-carboxyl labeled methyl benzoate by Hutchins, R. O.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1972**, *94*, 3268–3269.

PROPOSED ZWITTERIONIC MECHANISM



Scheme 8.

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8. Compound **14**: Mp: 128–130 °C. MS (API-ES, positive): *m/z* 327.9 $[MH]^+$. ^1H NMR (CD_3OD, 400 MHz): δ 7.78 (s, 1H), 7.62–7.60 (m, 3H), 7.45–7.42 (m, 2H), 7.15 (s, 1H), 3.78 (s, 3H). HRMS (DEI): calcd for $C_{12}H_{10}NO_2I$ $[M]^+$ *m/z* 326.9756, found 326.9750.
9. Compound **15**: MS (API-ES, positive): *m/z* 203.1 $[MH]^+$. ^1H NMR (CD_3OD, 400 MHz): δ 7.82 (s, 1H), 7.65–7.53 (m, 5H), 6.59 (s, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 150.5, 143.5, 136.3, 130.2 (2C), 128.4, 122.8 (2C), 120.6, 116.0, 56.2. HRMS (DCI): calcd for $C_{12}H_{11}{}^2HNO_2$ $[MH]^+$ *m/z* 203.0931, found 203.0928.
10. Compound **16**: MS (API-ES, positive): *m/z* 342.3 $[MH]^+$. Mp: 136–138 °C. ^1H NMR (CD_3OD, 400 MHz): δ 7.60–7.50 (m, 3H), 7.46 (s, 1H), 7.35 (t, J = 6.6 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 6.95 (s, 1H), 6.91–6.86 (m, 3H), 5.47 (s, 1H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 152.2, 148.5, 140.9, 138.7, 133.6, 129.8, 129.7, 129.4, 128.5 (2C), 128.3 (2C), 127.5, 127.3, 123.7, 115.0, 70.3, 56.2. HRMS (FAB): calcd for $C_{19}H_{17}NO_3Cl$ $[MH]^+$ *m/z* 342.0899, found 342.0910.
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