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Pyrrole Derivatives of 6-APA and 7-ACA. Oxygenation by Singlet Oxygen

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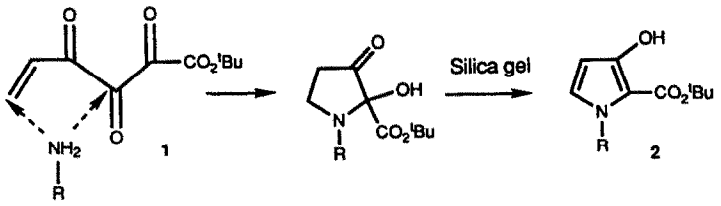
Abstract: Reactions of the primary amino groups of 6-APA and 7-ACA esters with a vinyl tricarbonyl derivative generate substituted pyrroles at the 6- and 7- positions. Studies on the singlet oxygen oxygenation of one of these pyrrole derivatives are reported.

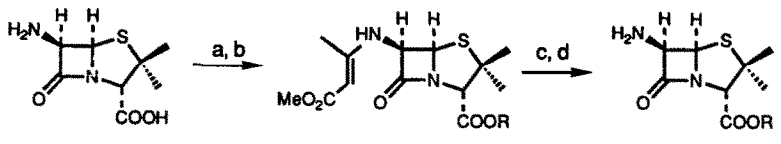
We have previously shown that primary amines of widely varying composition take part in smooth, tandem addition to the vinyl tricarbonyl reagent **1** to form hydroxypyrrolidinone esters which undergo silica gel-promoted dehydration to 3-hydroxypyrrole-2-carboxylic acid esters **2** (Scheme 1).[1] These pyrrole derivatives are of interest because of the mild conditions of their formation and their potential use as intermediates in synthesis. For example, reacting as tautomers of β-keto esters, they undergo alkylation at the 2-position,[2,3] and with singlet oxygen, they are readily transformed to vinylogous amides and other products of oxygenation.[4] In this communication, we describe our studies on the formation of pyrrole derivatives from the reactions of **1** with the amino β-lactams, 6APA **3** and 7-ACA, **7**, as well as the further conversion of these pyrrolo derivatives to oxygenated products by the action of singlet oxygen. Earlier work on the formation of related unsubstituted pyrrole derivatives has been reported by Nudelman[5] and Chan.[6]

Scheme 1



In the form of the free carboxylic acid, **3** failed to give the product of tandem addition with the vinyl tricarbonyl reagent **1**. We therefore esterified the carboxyl group using the general procedure of Ikeda.[7] Thus, protection of the amino group as the enamine with methyl acetoacetate/triethylamine and then treatment with benzyl bromide or allyl bromide in the presence of NaI/$KHCO_3$ yielded the benzyl or allyl esters, **4a,b**. Deprotection of the amine with *p*-toluenesulfonic acid followed by bicarbonate yielded the amino esters **5a,b** (Scheme 2).

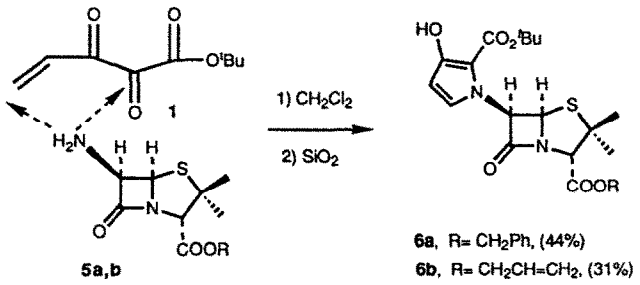
Scheme 2



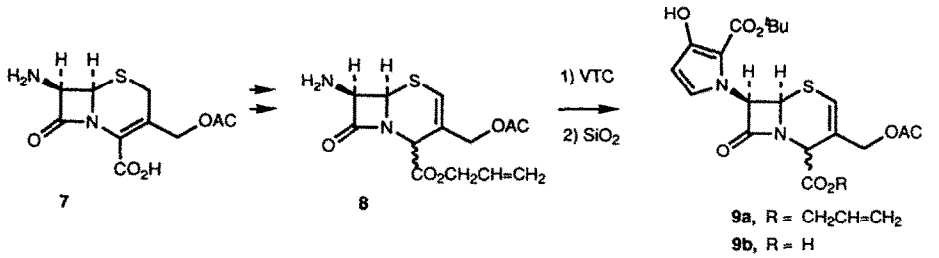
(a) $CH_3COCH_2CO_2CH_3$, Et_3N, CH_2Cl_2, CH_3OH. (b) $KHCO_3$, NaI, RBr, EtOAc, DMF. (c) p-TsOH·H_2O, EtOAc. (d) $NaHCO_3$.

The reactions of the esters **5a and 5b** with the vinyl tricarbonyl reagent **1** (VTC) took place smoothly at 0° in methylene dichloride followed by treatment with silica gel at room temperature to form the 6-pyrrolo derivatives **6a** (44%, benzylester) and **6b** (31%, allyl ester) (Scheme 3). Similar reaction of the tricarbonyl reagent **1** with **8a**, an allyl ester of 7-ACA, **7**, yielded the 7-pyrrolo derivative **9** (Scheme 4). Both **6a**, **6b** and **9** could be readily converted to the corresponding sulfoxides by the action of MCPBA.

Scheme 3

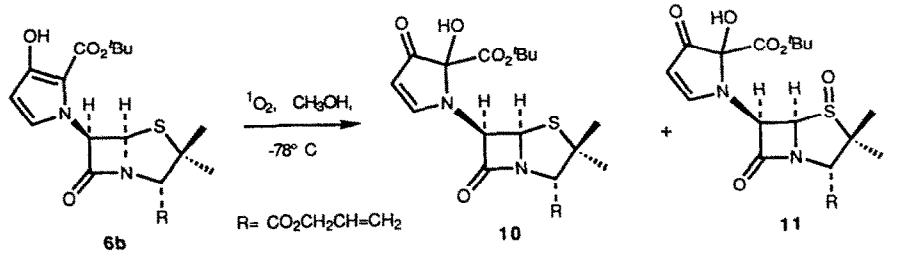


Scheme 4

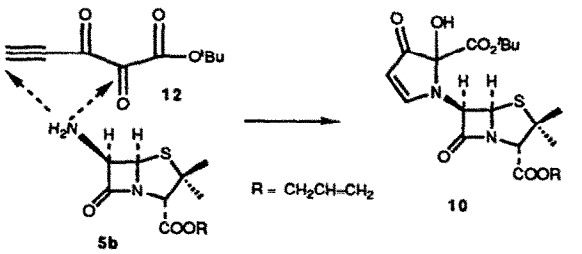


3-Hydroxypyrrole 2-carboxylates of type **6** have been shown to undergo ready reaction with singlet oxygen to form oxygenated products incorporating functionality not readily accessible by conventional transformations.[4] We were particularly interested in preparing novel oxygenated derivatives at the 6-position of 6-APA in this way, and accordingly, explored the dye-sensitized photooxidation of compound **6b** in methanol as described below.

Scheme 5



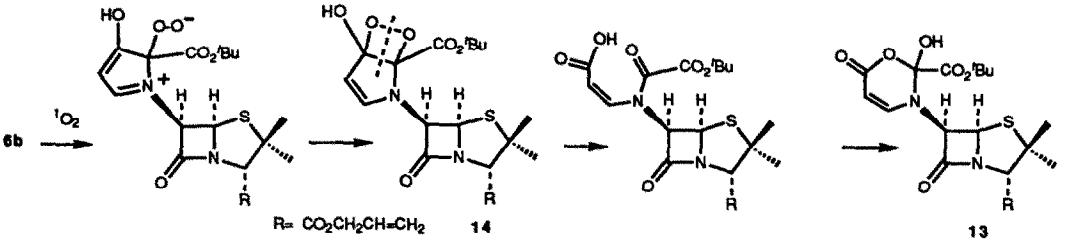
Using methylene blue as the sensitizer at -78 °C, under irradiation with a 650 watt Sylvania flood light for 1 hr, compound **6b** was converted by singlet oxygen to the keto carbinolamine **10** (42%). A small amount of the sulfoxide **11** was formed concurrently (Scheme 5) along with other more polar byproducts which were not isolated. The assignment of structure **10** to the oxidation product was based on the ^1H NMR, IR and mass spectrum. The latter showed a peak at m/e=439 in accord with molecular formula $C_{20}H_{27}N_2O_7S$ corresponding to the uptake of one atom of oxygen. This assignment was confirmed by an independent synthesis of **10** involving the addition of the 6-APA ester **5b** to the acetylenic tricarbonyl ester **12** (Scheme 6).[8]

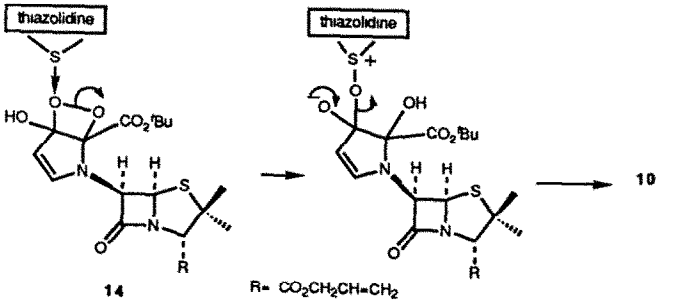


Scheme 6

Our previous experience in the photooxidation of hydroxypyrrole carboxylates[4] led us to expect the oxidative conversion of **6b** to the lactol **13** by the process outlined in Scheme 7. However, no evidence of **13** was found among the reaction products. It therefore appears most likely that the pyrrolinone t-butyl carboxylate **10** was formed from the dioxetane intermediate **14** which underwent deoxygenation by attack of the sulfide grouping in the thiazolidine ring (Scheme 8). This deoxygenation could take place by either an intermolecular process as shown, or by an intramolecular alternative.[10]

Scheme 7





Scheme 8

Earlier work showed that diphenyl sulfide, though inactive towards $^1O_2$, is an efficient scavenger of oxygen from dioxetanes.[9] In the present study, we found that addition of diphenyl sulfide, to the photooxidation reaction resulted in an enhanced yield of **10** (67%). A control study also revealed that the BOC-derivative of 6-APA could be recovered unchanged when exposed to $^1O_2$ under the above conditions of dye-sensitized photooxidation. This finding is in accord with the view that the sulfoxide **11** isolated in the conversion of **6b** to **10** is formed by thiazolidine sulfide-deoxygenation of the peroxidic intermediate **14** rather than by direct reaction with $^1O_2$.

The free acid **6c** derived from the 6-APA pyrrolo derivative has been tested for antibacterial activity by Dr. J.L. Roberts of Hoffmann-La Roche. This product was found to be inactive in Mueller-Hinton Agar tests against standard organism screens.

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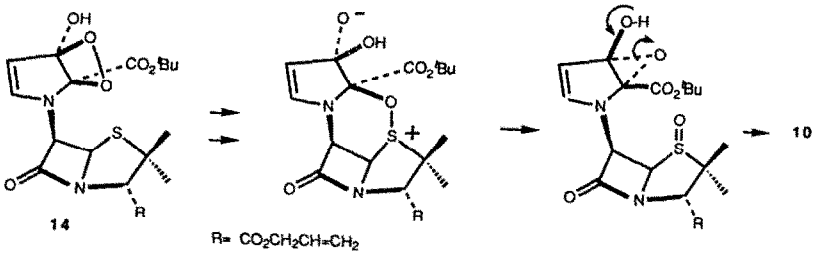
References

1) Wasserman, H.H; Cook, J.D.; Fukuyama, T.M.; Rotello, V.M. *Tetrahedron Lett.* **1989**, *30*, 1721
2) (a) Chong, R.; Clezy, P. S. *Aus. J. Chem.* **1967**, *20*, 935. (b) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1978**, *26*, 2224. (c) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1978**, *26*, 3521. (d) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1979**, *27*, 1448. (e) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Kobayashi, H.; Takano, S. *Heterocycles* **1981**, *15*, 843.
3) Wasserman, H.H.; Vu, C.B.; Cook J.D. *Tetrahedron* **1992**, *48*, 2101-2112.
4) Wasserman, H.H.; Frechette, R.; Rotello, V.M.; Schulte, G. *Tetrahedron Letters* **1991**, *32*, 7571.
5) Nudelman, A; Braun, F; Karoly, E. *J. Org. Chem.* **1978**, *43*, 3788.
6) Chan, T.H; Lee, S.D. *J. Org. Chem.* **1983**, *48*, 3059.
7) Ikeda, S; Sakamoto, F; Kondo, H; Moriyama, M; Tsukamoto, G. *Chem. Pharm. Bull.* **1984**, *32*, 4316.
8) Wasserman, H.H.; Frechette, R.; Oida, T.; Van Duzer, J.H. *J. Org. Chem.* **1989**, *54*, 6012.
9) Wasserman, H.H.; Saito, I. *J. Am. Chem. Soc.* **1975**, *97*, 905.
10) Intramolecular transfer of oxygen from the dioxetane **14** could take place according to Scheme 9.



Data on new products: **For 6a:** ^{1}HNMR: 1.39(s, 3H), 1.56(s, 3H), 1.58(s, 9H), 4.52(s, 1H), 5.20(s, 2H), 5.68 (br, 1H), 5.80(d, 1H, J=3.3 Hz), 6.04(br, 1H), 7.03(br, 1H), 7.39(s, 5H). IR: 3460, 1790, 1750, 1695, 1645, 1560 cm^{-1}; HRMS: calcd. for $C_{24}H_{29}N_2O_6S$ m/e 473.1748 , found m/e 473.1781.

For 6b: ^{1}HNMR: 1.48(s, 3H), 1.60(s, 12H), 4.52(s, 1H), 4.70(br, 2H), 5.32(br, 1H), 5.40(br, 1H), 5.73(br, 1H), 5.82(d, 1H), 5.95(m, 1H), 6.08(br, 1H), 7.05(br, 1H). IR: 3460, 3140, 1785, 1745,
1690, 1640, 1560 cm^{-1}. HRMS: calcd. for $C_{20}H_{27}N_2O_6S$ m/e 423.15911, found m/e 423.1592.

For 6c: ^{1}HNMR: 1.57(s, 3H), 1.60(s, 9H), 1.64(s, 3H), 4.52(s, 1H), 5.69(br, 1H), 5.81(d, 1H, J=3.2 Hz), 6.09(br, 1H), 7.04(br, 1H). IR: 3440, 3500-2500, 1780, 1740, 1690, 1640, 1550 cm^{-1}. HRMS: calcd. for $C_{17}H_{23}N_2O_6S$ m/e 383.12779, found m/e 383.1256. **For 9a:** ^{1}HNMR: 1.61(s, 9H), 2.08(s, 3H), 4.58(d, 1H, J=12.7 Hz), 4.68(dm, 2H, J=6.0 Hz), 4.73(d, 1H, J=12.7 Hz), 5.13(d, 1H, J=1.6 Hz), 5.32(dm, 1H, J=10.4 Hz), 5.37(dm, 1H, J=17.1 Hz), 5.44(br, 1H), 5.83(d, 1H, J=3.1 Hz), 5.94(m, 1H), 6.07(br, 1H), 6.41(br, 1H), 6.95(br, 1H). IR: 3450, 3130, 1780, 1740, 1685, 1640, 1555 cm^{-1}. HRMS: calcd. for $C_{22}H_{27}N_2O_8S$ m/e 479.14891, found m/e 479.1507.

For 9b: ^{1}HNMR: 1.61(s, 9H), 2.11(s, 3H), 4.63(d, 1H, J=12.8 Hz), 4.80(d, 1H, J=12.8 Hz), 5.15(s, 1H), 5.45(br, 1H), 5.84(d, 1H, J=3.0 Hz), 6.09(br, 1H), 6.43(s, 1H), 6.95 (br, 1H). IR: 3440, 3500-2500, 1780, 1745, 1690, 1645, 1560 cm^{-1}. HRMS: calcd. for $C_{19}H_{23}N_2O_8S$ m/e 439.11759, found m/e 439.1157.

For 10: mp 47-50°C; R_f 0.39; IR (neat) 3430, 3120, 1790, 1740, 1695, 1545 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.48 (s, 9H, *t*-Butyl), 1.54 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 4.50 (s, 1H, H_3), 4.67 (d, 2H, J = 6.0 Hz, OCH_2), 4.74 (s, 1H, OH), 5.15 (d, 1H, J = 4.0 Hz, COCH=C-N), 5.22 (d, 1H, J = 3.8 Hz, H_5), 5.31 (br d, 1H, J = 10.2 Hz, cis-C=CH), 5.38 (br d, 1H, J = 18.3 Hz, trans-C=CH), 5.40 (d, 1H, J = 3.8 Hz, H_6), 5.92 (m, 1H, HC=C), 8.10 (d, 1H, J = 4.0 Hz, COC=CH-N); ^{13}CNMR ($CDCl_3$) δ 27.68, 30.50, 61.39, 65.53, 66.35, 68.76, 70.91, 85.35, 86.02, 97.49, 119.88, 131.00, 165.70, 166.19, 167.28, 171.65, 196.57; HRMS (FAB) calcd for $C_{20}H_{27}N_2O_7S$ 439.1540, found 439.1537.

For 11: R_f 0.21; IR (neat) 3400, 1790, 1740, 1610, 1065 cm^{-1}; ^{1}HNMR ($CDCl_3$) 1.35 (s, 3H, CH_3), 1.50 (s, 9H, t-Butyl), 1.71 (s, 3H, CH_3), 4.42 (s, 1H, H_3), 4.72 (br d, 3H, OCH_2, OH), 4.81 (d, 1H, H_5), 5.35 (br d, 1H, cis-C=CH), 5.40 (br d, 1H, trans-C=CH), 5.45 (d, 1H, COCH=C-N), 5.55 (d, 1H, H_6), 5.93 (m, 1H, HC=C), 6.76 (d, 1H, COC=CH-N); MS (FAB) m/e 455 (6, M+H), 413 (4), 399 (27), 391 (58), 355 (12), 307 (13), 281 (30), 200 (47), 167 (100).