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OXIDATIVE TRANSFORMATION OF TRYPTOPHAN TO 3-(2-AMINOPHENYL)-2-PYRROLIDONE AND KYNURENINE

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Summary: Oxytryptophans 3, which are readily obtained by dye-sensitized photooxygenation of tryptophan followed by acid treatment, undergo a facile N,N'-transacylation to give the 3-(2-aminophenyl)-2-pyrrolidones 4 in the absence of oxygen, whereas in the presence of oxygen 3a was oxidized to kynurenine.

In our previous report[1], we described the first isolation of the tautomer of oxytryptamine, 3-(2-aminophenyl)-2-pyrrolidone by intramolecular transacylation. We also reported earlier that the dye-sensitized photooxygenation of L-tryptophan 1a led to the tricyclic hydroxide 2a[2], which is at the same oxidation level as oxytryptophan 3a. Indeed, 3a was obtained by treatment of 2a with 1N HCl(80-90°C, 45 min) in 76% yield[3], and could also be readily obtained from 1a by our modified DMSO oxidation[4] (conc HCl, 1.5 mole equiv., DMSO, 1.5 mole equiv., AcOH) in 92% yield. Similarly D,L-7-chlorooxytryptophan 3b was obtained from 2b in 89% yield, but DMSO oxidation of 1b failed to give 3b.

Recently, L- and D-tryptophans have been shown to be efficient precursors for the biosynthesis of pyrrolnitrin 14, and plausible biosynthetic pathways have been proposed.[5]

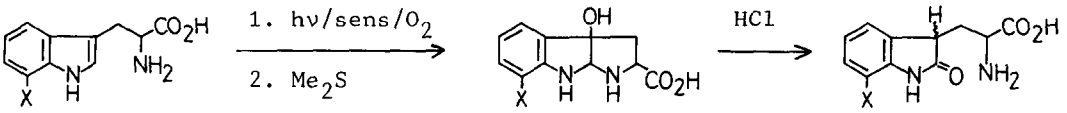
As an extension of our studies on the oxidation of tryptophan, we investigated the transformation of oxytryptophan 3 to 3-(2-aminophenyl)-2-pyrrolidone 4, which has the ring system required for pyrrolnitrin 14.

To an aqueous solution(80 ml) of 3a(5.5 mM) in argon atmosphere was added 10% NaOH(2.2 ml, 5.5 mM) and the reaction mixture was refluxed for 9.5 hr.[6] Direct isolation of 4b by acidification was unsuccessful and 4a readily reverted to 3a in acid. However, 4a was isolated when the reaction mixture was carefully neutralized by addition of ion exchange resin(Amberlite CG-50, COOH form) followed by lyophylization; 4a, λmax (H_2O) 232, 286 nm; λmax (KBr) 1600 cm^{-1}; δ(D_2O) 1.8-2.8(2H, m, CH_2), 3.4-4.1(2H, m, CH); m/z 220 M^+; positive diazo colour test. The structure of 4a was further confirmed by converting it to 5. Thus, treatment of the reaction mixture 4a with methyl

chloroformate and 10% NaOH followed by ion exchange column chromatography, lyophilization, and methylation with CH_2N_2 gave N,N'-transacylated product 5 as a mixture of two diastereomers which were separated by column chromatography to give less polar isomer **5a**(40% from **3a**) and more polar isomer **5b**(42% from **3a**).[7] Likewise, the benzyloxycarbonyl derivative **6** was obtained in 84% yield by treatment with Cbz-Cl and a similar work-up.[8]

The involvement of 7-chlorotryptophan as an intermediate at an earlier stage of the biosynthesis of **14** has been suggested.[9] In order to obtain chemical information we carried out the similar conversion of 7-chloro-oxytryptophan **3b** to the corresponding pyrrolidone 7. Treatment of **3b** and NaOH in H_2O(2 equiv., 12 hr, reflux) led to a mixture of two isomers **7a** and **7b** in 43% yield after a similar work-up as for **3a**.

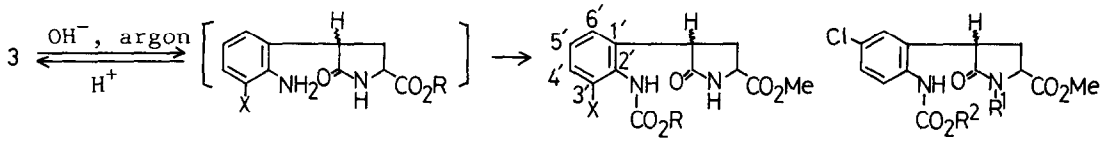
On the other hand, chlorination of the more polar isomer **6b** with t-BuOCl in CH_2Cl_2(3 equiv., 4.5 hr, r.t.) gave p-chlorinated compound **10b**(49%) and N-chloro derivative **11b**(45%).[10] The less polar isomer **6a** also gave **10a**(26%) and **11a**(59%). These results imply an alternative pathway for the biosynthesis of pyrrolnitrin.



1 a, X=H
b, X=Cl

2 a, X=H
b, X=Cl

3 a, X=H
b, X=Cl

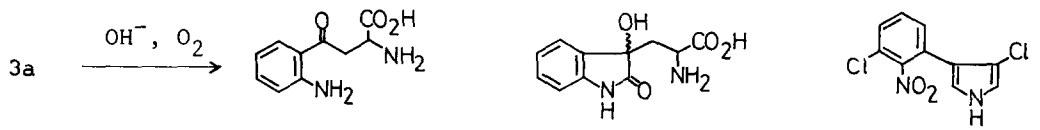


4 a, X=H, R=Na
b, X=H, R=H
c, X=Cl, R=Na

5, X=H, R=Me
6, X=H, R=Bzl
7, X=Cl, R=Me

8, R_1=H, R_2=Me
9, R_1=Cl, R_2=Me
10, R_1=H, R_2=Bzl
11, R_1=Cl, R_2=Bzl

(a, less polar isomer; b, more polar isomer)



12

13

14

Interestingly, when L-3a was treated with NaOH(10 equiv., 4 hr, r.t.) in oxygen atmosphere followed by Me_2S reduction, L-kynurenine 12(mp 161.5-164°C, 35% yield) and dioxytryptophan 13(46%) were obtained[11]. The similar reaction of 3a at elevated temperature(50-60°C, 20 min) raised the yield of L-kynurenine 12(61%, sole product). It is interesting to note that oxytryptophan 3a was once postulated as a biological intermediate between tryptophan 1a and kynurenine 12, but this pathway was excluded due to the fact that 3a was not metabolized to kynurenine.[12] However, the present results show that chemically, 3a readily converts to kynurenine.

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3. a) B. Witkop, Ann. 556, 103 (1944); b) W.E. Savige, Aust. J. Chem., 28, 2275 (1975). 3a, mp. 252-253°C(dec.), which was confirmed to be a mixture of two diastereomers by HPLC(t_R=12.5, 13.6 min: Nucleosil 5C-18, 10% H_2O in MeOH).
4. a) W.E. Savige, and A. Fontana, J. Chem. Soc., Chem. Comm., 599 (1976); b) K. Szabo-Pusztay, and L. Szabo, Synthesis, 276 (1979).
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6. The reaction was followed by HLPC and UV spectrum. The presence of two isomers of 4b was detected by HLPC(t_R=2.6, 3.3 min).
7. 5a, amorphous powder; λmax (EtOH) 231.5, 273sh nm; νmax (KBr) cm^{-1} 3260, 1710, 1525; m/z 292(M^+, 22), 260(100), 201(100); δ($CDCl_3$) 2.39 -3.06(2H, m, CH_2), 3.72, 3.77(6H, 2s, Me), 4.03(1H, t, J=7 Hz, CH), 4.37(1H, t, J=7 Hz, $C\underline{H}CO_2Me$), 6.94(1H, br.s, NH), 6.98-7.44(3H, m, arom.H), 7.61(1H, d, J=8 Hz, C_3,-H), 8.46(1H, br.s, ArNH).
   5b, mp 124-126°C; λmax (EtOH) 231.5, 272sh nm; νmax (KBr) cm^{-1} 3230, 1755, 1728, 1690, 1539, 1530; m/z 292(M^+, 24), 201(100); δ($CDCl_3$) 2.37-3.10(2H, m, CH_2), 3.74, 3.76(6H, 2s, Me), 3.99(1H, t, J=7 Hz, CH), 4.32(1H, t, J=7 Hz, $C\underline{H}CO_2Me$), 6.86(1H, br.s, NH), 7.03-7.42(3H, m, arom.H), 7.60(1H, d, J=8 Hz, C_3,-H), 8.36(1H, br.s, ArNH).
8. 6a, less polar isomer, mp 136.5-137°C; λmax (EtOH) nm(ε) 320sh(8140), 263sh(596), 268sh(528); νmax (KBr) cm^{-1} 3300(NH), 1738, 1710, 1688(CO), 1520; m/z 368(M^+), 91(100); δ($CDCl_3$) 2.35-3.00(2H, m, CH_2), 3.76(3H, s, Me), 3.99(1H, dd, J=10 Hz, J=7 Hz, CH), 4.33(1H, dd, J=8 Hz, J=6 Hz, $C\underline{H}CO_2Me$), 5.18(2H, s, CH_2Ar), 6.85(1H, br.s, NH), 7.05-7.54(8H, m, arom.H), 7.67(1H, d, J=7 Hz, C_3,-H), 8.52(1H, br.s, ArNH); CD(c=5.25 x

10^{-4}, MeOH) [θ](nm) +3.1 x 10^4 (233).
6b, more polar isomer, mp 161-162°C; λmax (EtOH) nm(ε) 229sh(8060), 263sh(564), 268sh(493); νmax (KBr) cm^{-1} 3210br(NH), 1754, 1725, 1685(CO), 1527; m/z 368(M^+), 91(100); δ($CDCl_3$) 2.31-2.98(2H, m, CH_2), 3.73(3H, s, Me), 3.95(1H, t, J=9 Hz, CH), 4.22(1H, t, J=7 Hz, $\underline{CH}CO_2Me$), 5.16(2H, s, $ArCH_2$), 6.72(1H, br.s, NH), 7.02-7.49(8H, m, arom.H), 7.62(1H, d, J=7 Hz, C_3,-H), 8.42(1H, br.s, ArNH); CD(c=5.31 x 10^{-4}, MeOH) [θ](nm) +1.6 x 10^4 (216), -2.8 x 10^4 (237).

9. O. Salcher and F. Lingens, Tetrahedron Lett., 3097, 3101 (1978).
10. **10b**, mp 134-134.5°C; λmax (EtOH) nm(ε) 239(10800), 277(580); νmax (KBr) cm^{-1} 3230(NH), 1758, 1737, 1690(CO); m/z 404(M^++2), 402(M^+).
11b, amorphous powder; λmax (EtOH) 236, 283sh nm; νmax (KBr) cm^{-1} 3320(NH), 1720(CO); m/z 436(M^+); positive KI-starch test. Reduction of **11b** with $NaBH_4$ or Me_2S gave **10b**.
11. For the mechanism see reference 1). The structure of L-kynurenine **12** was confirmed by comparison with the authentic sample prepared by O_3 oxidation of L-tryptophan.
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