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REACTIVITY OF OXYTRYPTAMINE
CONVERSION TO 3-(o-AMINOPHENYL)-2-PYRROLIDONE AND KYNURENAMINE

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Summary : Oxytryptamine 1 was converted to kynurenamine 5, benzoxazinone 6, and 3-hydroxy derivative 7b in NaOH-MeOH in the presence of oxygen, whereas 1 undergoes N,N'-transacylation to give the isomeric product 4 in argon atmosphere.

Oxytryptamine, 3-(2-aminoethyl)-2-indolinone, 1, has been known to be unstable as a free base. Attempts to synthesize 1 in free form met with no success and gave a complicated mixture of unidentified products[1]. Thereby, 1 has been prepared as its salt form such as hydrochloride. The instability of 1 has been ascribed to its transformation to 3-(o-aminophenyl)-2-pyrrolidone 4 by intramolecular acyl migration. However, while the conversion of oxytryptamine derivatives to the corresponding isomeric 2-pyrrolidones is precedented[2-5], the isolation of 4 itself has not been demonstrated. In earlier report[6], it was shown that by refluxing 1 in 2N sodium hydroxide under nitrogen, the oxindole ring was opened to give α-(o-aminophenyl)-γ-aminobutyric acid 3, which was isolated as bisbenzyloxycarbonyl derivative.

We now report the first successful isolation of 3-(o-aminophenyl)-2-pyrrolidone 4 and an unreported chemical property of oxytryptamine to kynurenamine.

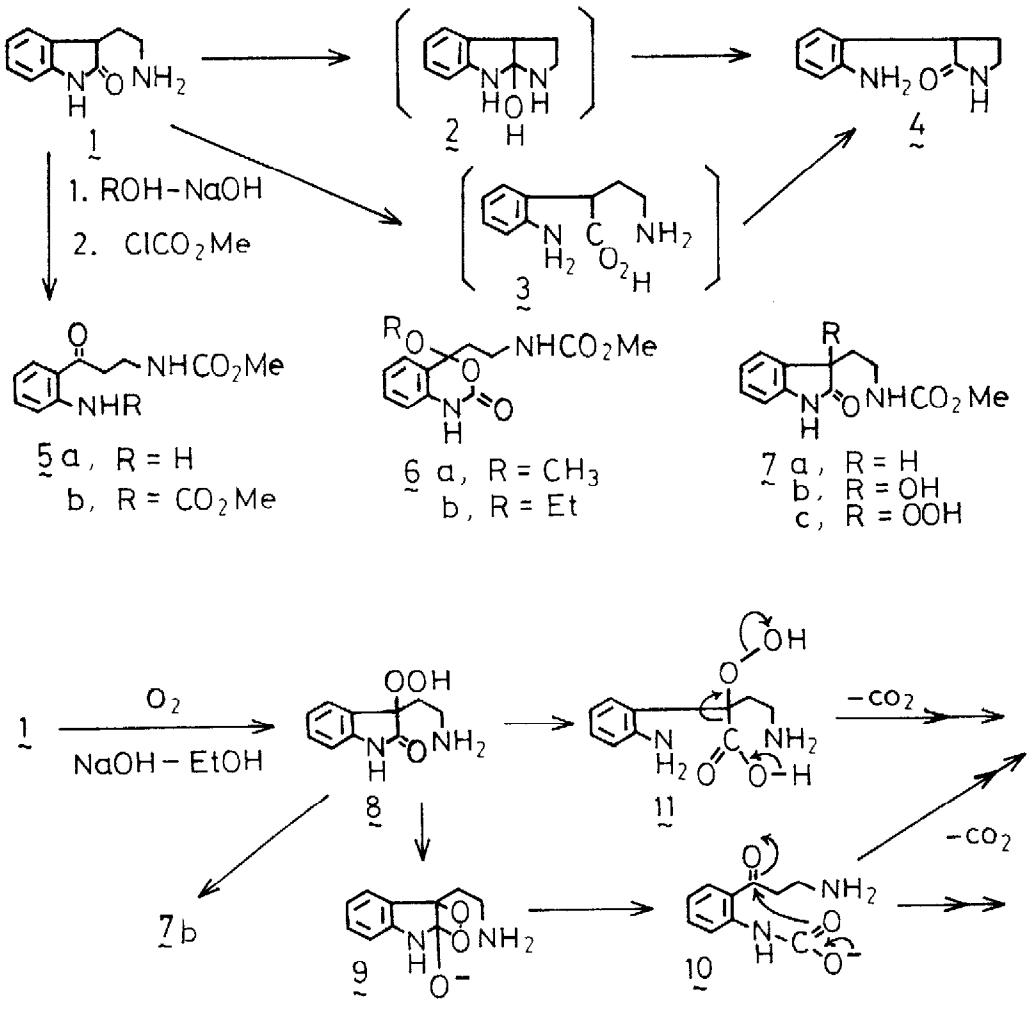
When an ethanolic solution of oxytryptamine hydrochloride 1·HCl was basified with 10% NaOH (10 mol equivalents) and the mixture was stirred for 1 hr at room temperature in an open air followed by treatment with methyl chloroformate[7], 3-hydroxy-2-indolinone 7b was obtained in 14% yield together with the two unexpected compounds, kynurenamine derivative 5a (3%) and 4H-3,1-benzoxazine derivative 6b (6%). No detectable amount of 4 was found in the reaction mixture. Instead, 1 was recovered in 43% yield as 7a. The similar reaction of 1 in methanol gave 5a (2%), 6a (3%), 7b (7%), and 7a (40%). The formation of these products implies that 1 has been oxidized by molecular oxygen under the reaction conditions.

Accordingly, under an oxygen atmosphere, the similar treatment of oxytryptamine hydrochloride for 15 min led to a 28% yield of 6b, 5a (13%), and 5b (2%). A trace of 7b was detected on TLC. The compound, 5a, was identical in all respects (IR, NMR, UV, mass spectra, mp, and TLC behavior) with a sample of the same structure produced by dye-sensitized photooxygenation of Nb-methoxycarbonyltryptamine[8]. The structure of 6a was confirmed on the basis of its spectral data and elemental analysis. 6a : mp 183-185°C (acetone), λmax (EtOH) 237 (ε 12900), 280 nm (1600) ; νmax (KBr) cm^{-1} 3250 (NH), 1730, 1695 (CONH), 1555 (CONH), 1030 ; δ (DMSO-d_6)2.00-2.30 (m, CH_2), 2.80-3.10 (m, CH_2N), 3.08 (s, OCH_3), 3.45 (s, CO_2CH_3), 6.80-7.50 (m, 5H, aromatic H and NH), 10.38 (s, NH) ; m/e 280 (3) M^+, 248 (3), 146 (100).

Furthermore, the prolonged treatment of 1 for 60 min under the similar condition and work-up yielded 5a as the main product in 31% yield, accompanied with a small amount of 5b (3%) and a trace of 6b. In contrast, when the reaction mixture was stirred for 60 min in nitrogen or argon atmosphere followed by the similar work-up, 1 was recovered as 7a in 71% yield and a small amount of 5a (2%), 5b (2%), and 6b (2%) were obtained. Compounds 5, 6, and 7 must, therefore, be formed by aireal oxidation, suggesting the instability of 1 might be associated with its susceptibility to triplet oxygen under alkaline conditions.

A possible pathway to account for the unexpected formation of 5, 6, and 7 is shown below, in which all the products are derived from the key intermediate 8[9]. Either cyclization of 8 to a dioxetane 9 which collapsed to 10 followed by subsequent decarboxylation or oxidative decarboxylation of 11 arised from the hydrolytic ring opening of 8 might result in the formation of 5. The formation of 6 can be envisioned to occur from 10 by intramolecular cyclization. This rationalization is supported by the conversion of 7c to 6, 5, and 7b.

Thus, a solution of 7a in anhydrous methanol was photooxygenated in the presence of Rose Bengal (1/100 mol equiv.) and MeONa (1/10 mol equiv.) for 6 hr (TLC, one spot corresponding to 7c). Neutralization with acetic acid followed by preparative TLC afforded the hydroperoxide 7c as amorphus in 33% yield, together with 6a (7%) and 5a (6%). 7c[10] : λmax (EtOH) 255, 294 nm ; νmax ($CHCl_3$) 3420, 3400-3100, 1710, 1620, 1520 cm^{-1} : δ ($CDCl_3$) 2.10 (m, CH_2), 3.18 (m, CH_2N), 3.52 (s, CO_2CH_3), 5.20 (broad s, NH), 6.80-7.40 (m, aromatic H), 9.10 (broad s, NH or OOH), 10.60 (broad s, OOH or NH) ; m/e 266 (1) M^+, 250 (11) M^+-O, 248 (3) M^+-H_2O, 234 (3) M^+-O_2, 149 (100). Reduction of 7c with dimethyl sulfide gave 7b. The oxygenation of 7a in a similar manner using equivalent molar of MeONa proceeded more rapidly (100 min) to give 7c. Without isolating 7c, subsequent treatment of this



reaction mixture with 10% NaOH for 30 min[11] yielded 6a (54%), 5a (9%), and a trace of 7b.

Isomeric transformation of 1 to 4 has been achieved by refluxing 1 with 10% NaOH (10 molar equivalents) in methanol under argon for 11 hr. Treatment of the reaction mixture with methyl chloroformate followed by preparative TLC furnished the desired 3-(o-aminophenyl)-2-pyrrolidone 4 in 30% yield, accompanied with 7a (28%) and 3a (7%). 4 : mp 120.5-121.5°C[12] (benzene) ; λmax (EtOH) 236 (ε 6900), 288 nm (2170) ; νmax (KBr) cm^{-1} 3410, 3335, 3220 (NH_2, NH), 1665 (CONH) ; δ ($CDCl_3$) 2.20-2.60 (m, CH_2), 3.30-3.60 (m, CH_2N), 3.76 (t, J = 8Hz, C_3-H), 4.20 (s, NH_2), 6.70 (m, 2H,

aromatic H), 6.90-7.40 (m, 3H, aromatic H and NH) ; m/e 176 (84) M^+, 159 (42), 146 (100). The compound 4 readily converts to the salt of oxytryptamine 1 within 1 hr by dissolving 4 in either 15% AcOH in MeOH or EtOH-5% HCl, which was followed by UV spectrum showing an isosbestic point at 293 nm as well as by TLC.

Thus, the present results suggest that the lability of 1 is probably due to the facile autoxidation rather than its isomerization to 4 and implicate an alternative pathway for the biosynthesis of pyrrolnitrin[13].

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References and Notes

1. J.B. Hendrickson, Thesis, Harvard University, 1954 and also see ref. 2-6.
2. E. Wenkert, B.S. Bernstein, and J.H. Udelhofen, J.Am.Chem.Soc., 80, 4899 (1958).
3. P.J. Islip and A.C. White, J.Chem.Soc., 1201 (1964).
4. E.E. van Tamelen, J.P. Yardley, M. Miyano, and W.B. Hinshaw, Jr., J.Am. Chem.Soc., 91, 7333 (1969).
5. P.An. Thio and M.J. Kornet, J.Heterocyclic Chem., 8, 479 (1971).
6. K. Freter, H. Weissbach, B. Redfield, S. Udenfriend, and B. Witkop, J.Am.Chem.Soc., 80, 983 (1958).
7. Neither the product nor the starting material 1 was isolated when acylation of the reaction mixture with methyl chloroformate was omitted.
8. M. Nakagawa, H. Okajima, and T. Hino, J.Am.Chem.Soc., 98, 632 (1976) ; idem., ibid., 99, 4424 (1977).
9. 3-Alkyloxindoles have been known to undergo facile autoxidation to the corresponding dioxindoles ; P.L. Julian et al (1952) in Heterocyclic Compounds,ed. R.C. Elderfield, John Wiley & Sons/New York, N.Y., pp 1-274.
10. The hydroperoxide 7c decomposes to 7b upon standing.
11. The reaction mixture gives a negative test for peroxide with acidified starch-iodide paper after 30 min.
12. Satisfactory elemental analysis was obtained.
13. M. Gorman and D.H. Lively in ''Antibiotics'' Vol. II, D. Gottlieb and P.D. Shaw, Ed., Springer-Verlag, New York, N.Y., 1967, pp 433 ; L.L. Martin, C.-J. Chang, H.G. Floss, J.A. Mabe, E.W. Hagaman, and E. Wenkert, J.Am.Chem.Soc., 94, 8942 (1972) ; C.-J. Chang, H.G. Floss, L.H. Hurley, M. Zmijewski, J.Org.Chem., 41, 2932 (1976).

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