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A PHOTOCHEMICAL SYNTHESIS OF 4-HYDROXYINDOLE[1]

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1-Alkoxycarbonyl-4-hydroxyindoles were prepared in ca. 25% yields from 5-(alkoxycarbonylamino)isoquinoline 2-oxides by irradiation in an aprotic solvent, followed by an acid treatment under solvolytic conditions. 1-Benzyloxycarbonyl-4-hydroxyindole was then converted to the title compound by catalytic hydrogenation.

We wish to report a convenient and efficient synthesis of 4-hydroxyindole (11) and its 1-alkoxycarbonyl derivatives (6), useful intermediates for the synthesis of physiologically active indoles having an oxygen function at the 4-position,[2] from 5-(alkoxycarbonylamino)isoquinoline 2-oxides (1).[3] Three synthetic routes to 4-hydroxyindole (11) have been available starting from either 2-hydroxy-6-nitrotoluene,[4] 2-hydroxy-6-nitrobenzaldehyde,[5] or 6,7-dihydroindol-4(5H)-one.[6] However, none of them seems to be satisfactory due to tedious and many step procedures for their conversions to the aimed indole (11).

Our previous finding that the 1,3-benzoxazepine, derived photochemically from 1-cyano-3-methylisoquinoline 2-oxide, afforded 2-hydroxyphenylacetone by an acid hydrolysis[7] has led us to a new two step synthesis of 1-(alkoxycarbonyl)-4-hydroxyindoles (6) from the N-oxides (1) which can be carried out successively without any isolation and purification of the intermediates; (i), the N-oxide (1) was first irradiated in an aprotic solvent at ≥300 nm[8] until the disappearance of 1 then (ii), the crude products, which consist mainly of the oxazepine[9] (3) and isocarbostyril species (10) obtained after evaporation of the solvent, were refluxed in methanol containing 10% aq. sulfuric acid for 10 hr. Silica gel column chromatography separated the products, the benzofuran[10,11] (9), the hydroxyindole[12] (6) and the isocarbostyril[13] (10) as summarized in the Table. The isocarbostyril (10) became

Table. Products from 1 after Irradiation* (i) and Solvolysis** (ii).

Compound	6	9	10
a	mp 119-120° (27-32%)	mp 120-123° (4-5%)	mp 231-234° (22-29%)
b	mp 121-124° (21-26%)	mp 95-97° (9-13%)	mp 247-249° (17-28%)

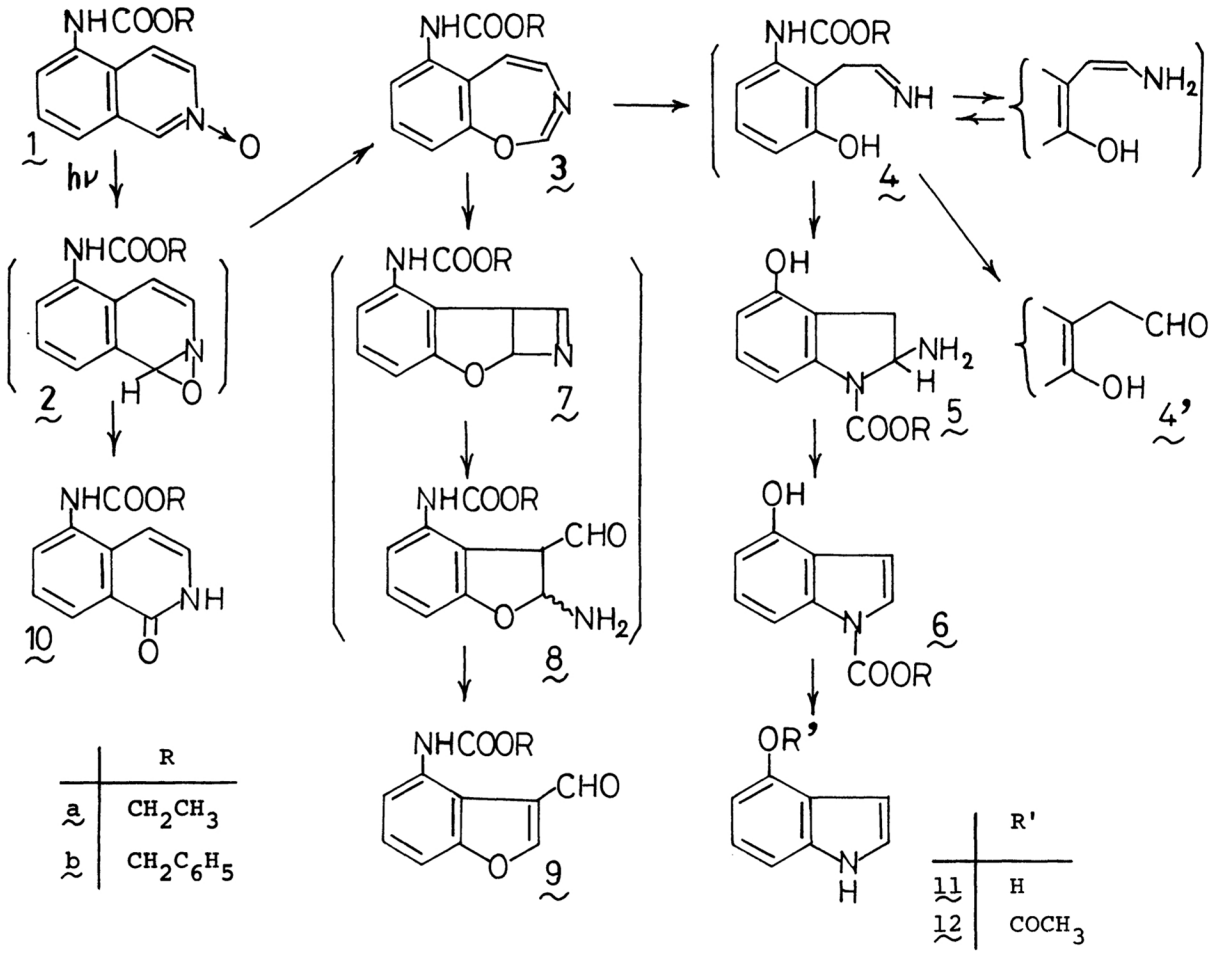
* Irradiation was carried out in acetone (ca. 3.35 mM solution of 1).

** Solvolysis of the photo-products was carried out under the condition ii.

the sole rearrangement product, when the irradiation was performed in methanol. Taking this fact as well as known photo-isomerization reactions of aromatic amine oxides[14] into consideration, the formation of 10 is explained by a carbonium ion rearrangement of an oxaziridine species[15] (2) formed as a primary photo-product from 1. The oxazepine (3) which is expected to be formed preferentially by the photolysis in an aprotic solvent of 1 via 1,5-oxygen shift of 2 accounts for the formation of the other two products (9 and 6). Thus, the benzofuran (9) would be formed by the hydrolysis of the 2a,7a-dihydrobenzofuro[2,3-b]-azete[16] (7) derived photochemically from 3. A direct solvolysis of the oxazepine (3) under the acidic condition (ii) can reasonably account for the formation of the indole (6), because analogous pathways from the related oxazepines to the ring opened products (e.g., 4 and 4') are well known.[7, 16a,b] Furthermore, the proposed mechanism for the formation of the indole (6) from 3 was confirmed by an actual isolation of 2-amino-2,3-dihydro-1-ethoxycarbonyl-4-hydroxyindole[17] (5a) from the photo-products of 1a after a mild hydrolysis (warmed at 60° in methanol containing 10% aq. hydrochloric acid for 2 hr) and its subsequent transformation to the indole (6a) under the condition ii.

Catalytic reduction of the indole (6a) over palladium-charcoal afforded 4-hydroxyindole[18] (11) in ca. 75% yield.

It should be noted that, while 4-hydroxyindole is a quite unstable compound,[5] these 1-alkoxycarbonyl-4-hydroxyindoles (6) were stable crystalline compounds. Hence, 1-benzyloxycarbonyl-4-hydroxyindole (6b) prepared for the first time in the present study fits to manipulations of its 4-hydroxy function, because at the final manipulation stage, the benzyloxycarbonyl function can be eliminated by the catalytic hydrogenation.



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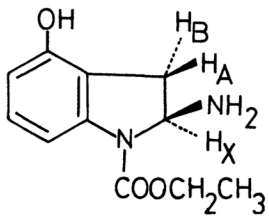
References and Notes

1. This paper forms Part XXXV of "Studies on the N-oxides of π-deficient N-heteroaromatics." Part XXXIV: C. Kaneko, H. Fujii, S. Kawai, A. Yamamoto, K. Hashiba, T. Kimata, R. Hayashi, and M. Somei, Chem. Pharm. Bull., 28 (1980), in the press.
2. 4-[2-Hydroxy-3-(isopropylamino)propoxyindole[a] (vasodilator known by the commercial name, Pindolol) as well as Psilocybin (4-phosphoryloxy-N,N-dimethyltriptamine) and its 4-hydroxy derivative (Psilocin), both of which are the hallucinogenic constituents[b] of the mashroom; Psilocybe mexicana, are the typical indoles belonging to this class: a) F. Troxler, Swiss Pats., 469002 and 472402 (both 1969 to Sandoz); b) A. Hofmann, R. Heim, A. Brack, H. Kobel, A. Frey, H. Ott, T. Petrzilka, and F. Troxler, Helv. Chim. Acta, 42, 1557 (1957).
3. Obtained by the N-oxidation of the corresponding bases with hydrogen peroxide-acetic acid.[a] These bases were prepared from 5-aminoisoquinoline[b] by the usual alkoxycarbonylation. a) E. Ochiai, "Aromatic Amine Oxides", Elsevier, Amsterdam, 1967, pp. 24-26; b) M. Somei, K. Kato, and S. Inoue, Chem. Pharm. Bull., in the press.

4. A. Stoll, F. Troxler, J. Peyer, and A. Hofmann, Helv. Chim. Acta, 38, 1452 (1955).
5. R.J.S. Beer, K. Clarke, H. Khorana, and A. Robertson, J. Chem. Soc., 1948, 1605.
6. H. Plieninger and K. Klinga, Chem. Ber., 101, 2605 (1968); D.B. Repke, N.J. Ferguson, and D.K. Bates, J. Heterocyclic Chem., 14, 71 (1977).
7. C. Kaneko, S. Yamada, and I. Yokoe, Tetrahedron Lett., 1966, 4701. See also, C. Lohse, J. Chem. Soc. Perkin II, 1972, 229.
8. Irradiation was performed by Toshiba 400P high-pressure mercury lamp with Pyrex filter.
9. Attempts to isolate 3a,b were unsuccessful. 2-Phenyl- and 2-cyano-1,3-benzoxazepines are the only representatives of this ring system that have been isolated. 2-Unsubstituted oxazepines are known to be too unstable (towards solvolytic reactions) to isolate.[14]
10. All new compounds gave satisfactory combustion and/or mass spectrometric analysis and spectroscopic data consistent with the assigned structures.
11. The benzofuran (9b), δ ($CDCl_3$): 5.20, s (2H), 6.9-7.5, m (7H), 8.07, s (H-2), 8.14, d,d, J=8.0 and 1.2 Hz (H-7), 9.7, s (CHO), and 10.2, br s, (NH); ν_{max}^{KBr} cm^{-1}: 3430, 1723, and 1668.
12. The indole (6b); δ (CD_3OD-$CDCl_3$ 1:9 v/v): 5.36, s (2H), 7.41, d, J=4.0 Hz (H-2), 6.66, d, J=4.0 Hz (H-3), 6.56, d, J=8.0 Hz (H-5), 7.05, t, J=8.0 Hz (H-6), 7.61, d, J=8.0 Hz (H-7), and 7.35, br s ($CH_2C_6H_5$). ν_{max}^{KBr} cm^{-1}: 3300,and 1745.
13. The isocarbostyril (10b); δ (DMSO-d_6): 5.15, s (2H), 7.10, d, J=7.2 Hz (H-3), 6.60, d, J=7.2 Hz (H-4), 7.2-8.1, m (8H), 9.40, br s and 11.0 br s (both NH); ν_{max}^{KBr} cm^{-1}: 3450, 3350, 1693, and 1660.
14. a) C. Kaneko, Yukigosei Kyokaishi, 26, 758 (1968); M. Ishikawa and C. Kaneko, Kagaku no Ryoiki, Suppl.92, 149 (1970); c) G.G. Spence, E.C. Taylor, and O. Buchardt, Chem. Rev., 70, 231 (1970); d) F. Bellamy and J. Streith, Heterocycles, 4, 1391 (1976).
15. The oxaziridine was detected spectroscopically at 77° K by photolysis of 6-cyanophenanthridine 5-oxide: K. Tokumura, M. Itoh, and C. Kaneko, Tetrahedron Lett., 1979, 2027.
16. Photochemical formation[a,b] of this species from 1,3-benzoxazepines and their subsequent conversion[b] to benzofuran derivatives under solvolytic conditions have been reported. a) C. Lohse, Tetrahedron Lett., 1968, 5625; b) J.B. Bremner and P. Wiriyachitra, Aust. J. Chem., 26, 437 (1973).
17. The indoline (5a) was obtained as a crystalline hydrochloride, mp 156-158°. δ (CD_3OD): 1.41, t, J=7.0 Hz (CH_3), 4,36, q, J=7.0 Hz (CH_2), 6.4-7.3, m (3H), 2.8-4.0, m (H-A and H-B), and 5.71, d,d, J_{AX}=3.0 and J_{BX}= 8.0 Hz (H-X).



18. Physical and spectroscopic data of 4-hydroxyindole, 11 (mp 97-99°) and its acetate, 12 (mp 98-100°), were identical with those reported.[4-6]

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