PHOTOREACTION OF THIOBENZAMIDE WITH 2-VINYLFURAN ANALOGUES. FACILE SYNTHESIS OF TETRACYCLIC INDOLE SYSTEM.[#,1]

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Abstract----Photoreaction of thiobenzamide (**1**) with 2-vinylfuran analogues (**2**) in benzene solution gives 1*H*-benzo[*g*]furo[2,3-*e*]indole derivatives (**3**,**5**).

The indole alkaloids are a very large family of natural products, and the syntheses of various indole systems have received considerable attention.[2] Although numerous synthetic routes to indole systems are well known, little is known about the facile synthetic route to multicyclic indole system such as 1*H*-dibenz[*e*,*g*]indole and 1*H*-benzo[*g*]thieno[2,3-*e*]indole, partly because the starting materials are not always available. With respect to the construction of the multicyclic indole system, Moskal and van Leusen reported the synthetic method by electrocyclic ring closure of dialkenylpyrroles which are derived from 1-tosylalkenyl isocyanides and Michael acceptors.[3] Recently, the multicyclic indole system, 1*H*-dibenz[*e*,*g*]indole skeleton, was demonstrated as a new potential DNA intercalative drug delivery vehicle.[4]

As part of a continuing study on the photochemistry of arenecarbothioamide systems with olefins (Paterno-Büchi acceptor),[5-11] we have reported that certain furans (as an olefin analogue) serve as three-carbon annulation unit for multicyclic ring systems.[11] As an extension of this work, the generality of transformation of furans having an unsaturated α-substituent conjugated with a ring was investigated. In this paper we wish to report the facile synthesis of tetracyclic indole system through photoreaction of thiobenzamide (**1**) with 2-vinylfuran analogues (**2**).

In order to examine whether exocyclic double bond in furan participates or not in annulation units, 2-furanacrylic

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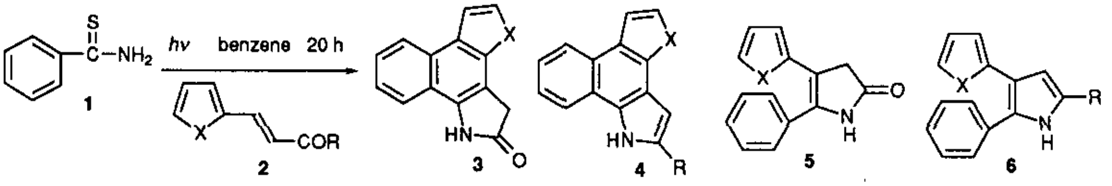
[#]This paper is dedicated to the memory of the late Professor Yoshio Ban.

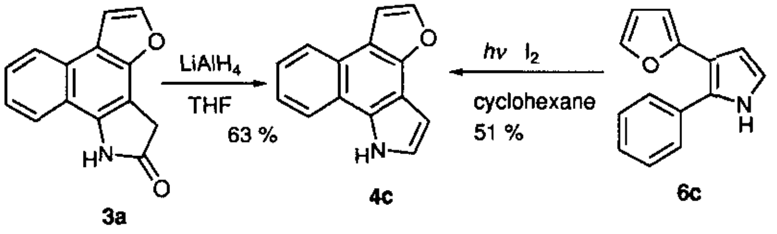
acid (**2a**) readily available was first selected as olefin-conjugated furan. As preliminary experiment, photolysis of thiobenzamide (**1**) with 2 eq. of **2a** was carried out in benzene using a high pressure mercury lamp through a Pyrex filter under N_2 atmosphere. As a result, the tetracyclic compound (**3a**) was obtained in 20% yield, along with the photodimer of **2a**, arised from cyclobutane, in 18% yield. To avoid the formation of photodimer of **2a**, the molar ratio of **1** and **2a** was varied. As a result, the yield of **3a** increased to 39% with the ratio of 2 : 1 (Table 1).

Table 1. Photoreaction of **1** with **2**.



2a X=O R=OH	**3a** 39 % (205 °C decomp.)		trace	
2b X=S R=OH	**3b** 32 % (275 °C decomp.)		**5b** 6 % (oil)	
2c X=O R=H		**4c** 31 % (mp 157-158 °C)		**6c** 6 % (oil)
2d X=O R=CH_3		**4d** 27 % (mp 161-162 °C)		**6d** 9 % (oil)

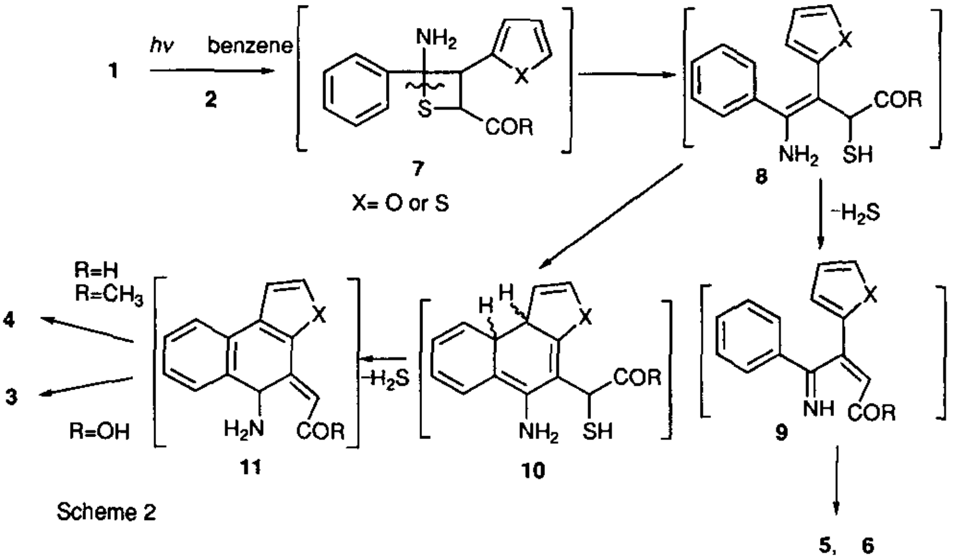
The structure of **3a** was assigned on the basis of elemental analysis and spectral data.[12] To further confirm the structure, **3a** was treated with $LiAlH_4$ to give reduction product (**4c**).[13] The structure of **4c** was established by comparison with a sample which was independently synthesized by the iodine-catalyzed photooxidation[14] of 2-phenyl-3-furanylpyrrole (**6c**),[15] that is, the physical and spectral data of **4c** photochemically derived from **6c** were identical with those of the reduction product (**4c**) (Scheme 1).



Scheme 1

Next, in order to examine the generality of this reaction, photoreaction of **1** with 2-thiopheneacrylic acid (**2b**) was performed under similar conditions as described above. As expected, the tetracyclic compound (**3b**) was obtained in 32% yield, accompanied by the pyrrolidone derivative (**5b**) in 6% yield. Similarly, in the cases of other 2-vinylfuran analogues (**2c,d**), the 1*H*-benzo[*g*]furo[2,3-*e*]indole derivatives (**4c,d**) were obtained in 27-31% yields, along with diarylpyrroles (**6c,d**) in 6-9% yields. Also the diarylpyrrole (**6d**) was easily transformed to **5d** by photolysis in the presence of iodine in 85% yield, but not transformed in the absence of iodine.

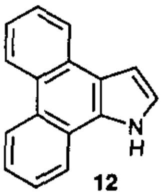
From these results, together with those reported in the previous papers,[5-11] the reaction pathway for the formation of tetracyclic indole system may be outlined as illustrated in Scheme 2. The reaction seems to proceed in several steps involving initial thietane (**7**) formation between thioamide and an exocyclic double bond of vinylfuran, leading to the vicinal-diarylethylene (**8**), which subsequently cyclized to give the tetracyclic compounds (**3**,**4**) since the conformation of the vicinal-diarylethylene intermediate (**8**)[16] is favorable for the photocyclization. Such an evidence of rigid conformation in favor of photocyclization is seen in some photoreactions.[16] But, in the case involving a loss of hydrogen sulfide in competition with cyclization of **8** to **10**, the intermediate (**8**) presumably leads to the diarylpyrrolidone (**5b**) or diarylpyrroles (**6c**,**d**) via **9**.



Scheme 2

As described above, 1*H*-dibenz[*e*,*g*]indole skeleton (**12**) was selected as a drug delivery vehicle on the basis of a variety of factors,[4] one of which is three or more fused coplanar aromatic rings for efficient intercalation to DNA, and the utility was demonstrated as the template in a potential DNA intercalating drug delivery system.[4]

Scheme 3



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In this study, the resulting tetracyclic indole system also can be offered as modified intercalative templates which possess two hetero atoms in the coplanar aromatic rings. Further, the present photoreaction would provide a new and convenient single-step convergent annulation approach for the construction of a multicyclic indole system, and is of both mechanistic and synthetic interest.

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12. **3a**: ir (nujol) 3250 (NH) and 1700 (amide carbonyl) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 3.36(2H, s, CH_2), 7.49(3H, m), 7.97(1H, m), 8.17(1H, m), 8.27(1H, m), 11.20(1H, br s, NH); ^{13}C nmr (DMSO-d_6) δ 34.3(t), 106.1(d), 117.0(s), 117.1(s), 122.8(d), 123.9(d), 124.2(d), 124.4(d), 126.1(s), 126.6(s), 137.7(s), 143.9(d), 148.1(s), 176.8(s); ms (*m/z*) 223(M$^+$). *Anal.* Calcd for $C_{14}H_9NO_2$: C, 75.32; H, 4.06; N, 6.28. Found; C, 75.13; H, 4.12; N, 6.24.
13. **4c**: ir (nujol) 3350 (NH) cm^{-1}; ^{1}H nmr (DMSO-d_6) δ 6.92(1H, m), 7.24(2H, m), 7.51(2H, m), 7.71(1H, m), 8.00(1H, m), 8.17(1H, m) 8.94(1H, br s, NH); ^{13}C nmr (DMSO-d_6) δ 100.7(d), 106.4(d), 113.4(s), 116.2(s), 120.2(d), 120.3(d), 122.5(d), 124.4(d), 124.5(s), 124.7(d), 125.4(s), 130.4(s), 148.4(s); ms (*m/z*) 207(M$^+$). *Anal.* Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.10; H, 4.53; N, 6.75.
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