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SYNTHESIS AND INTRAMOLECULAR PHOTOADDITION OF AN INDOLE QUINONEDIAZIDE

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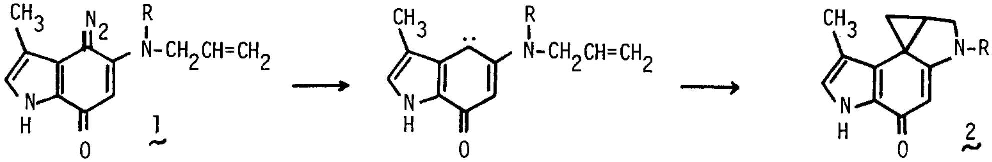
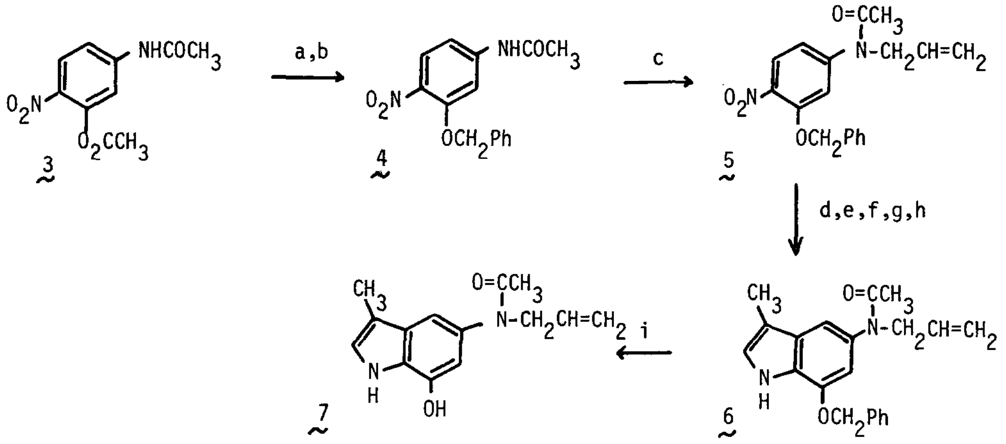
Summary An intramolecular carbenoid photoaddition route to the unique *spiro*-cyclopropane indol-7-one ring system of the antibiotic CC-1065 has been explored. The diazo transfer reaction of a 7-hydroxyindole intermediate leads *via* a 6-diazo intermediate to an isomeric ring system.

An intramolecular carbenoid addition provides a possible synthetic route to the unique spiro cyclopropane ring in the tetracyclic indol-7-one ring which is the locus of biological activity in the anti-tumor antibiotic CC-1065.[1]



An appropriately substituted 4-diazo-(4H)-indole-7-one (quinonediazide)[2], in turn, is a potential precursor of the carbenoid intermediate. Although intramolecular addition to alkenes involving benzenoid quinonediazides have not been encountered, the intermolecular reaction has been observed under both thermal and photochemical conditions.[3] Since quinonediazides derived from the indole ring have not previously been prepared, we have explored a synthetic route which has led to a quinonediazide which is isomeric with structure **1**, and have demonstrated that it undergoes intramolecular photoaddition.

The 7-hydroxyindole **7** was prepared in 25% overall yield from **3**[4] in nine steps with isolation of compounds **4**, **5** and **6** as intermediates. The conversion of **5** to **6** via reduction of the nitro group, diazotization, reduction to the hydrazine and Fischer indole cyclization with propionaldehyde proceeded smoothly without purification of the intermediates. The physical properties of the purified intermediates are as follows: **4** nmr peaks at 7.9(d), 7.8(NH), 7.2-7.6(m), 6.8(d of d), 5.25(s) and 2.2(s); mp: 131-132°. **5** nmr peaks at 7.9(d), 7.3(s), 7.0 (d of d), 5.7(m), 5.3(s), 5.1(m), 4.9(m), 4.3(d), and 1.9(s); mp: 156-157°. **6** nmr peaks at 8.55(NH), 7.4(m), 6.95(s), 6.41(d, J = 1 Hz), 5.85(m), 5.15(s), 4.8-5.2(m), 4.3(d), 2.30(s) and 1.82(s); mp: 138-140°. **7** nmr peaks at 9.3(NH), 6.97(s), 6.88(s), 6.43(s), 5.95(m), 5.0-5.2(m), 4.35(d), 2.30(s) and 1.98(s), mp 181-183°.



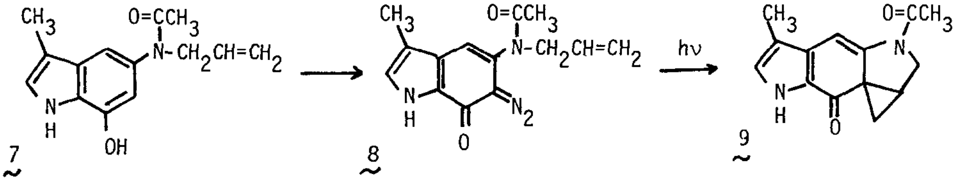
a: K_2CO_3, MeOH, 5 hr at 25°. b: K_2CO_3, KI, $PhCH_2Cl$, DMF, 4 hr at 25°. Yield 98%.

c: $KOCMe_3$, DMF, $CH_2{=}CHCH_2Br$, 24 hr at 25°. Yield 83%.

d: Zn, $CaCl_2$, EtOH, reflux 1.5 hr. e: HCl, $NaNO_2$, 0°. f: $SnCl_2$, HCl, -5°, 2 hr at 0°.
g: $CH_3CH_2CH{=}O$, DMF, 1 hr at 0°, NaO_2CCH_3, 5° for 18 hr. h: TsOH, THF, 8 hr at 25°. Yield 79%.

i: BBr_3, CH_2Cl_2, -40° for 2.5 hr. Yield: 40%.

Direct diazo transfer to phenols has been reported for α- and β-naphthol and for anthrone using *p*-toluenesulfonyl azide as the diazo transfer reagent.[5] Reactions of **7** involving amine-catalyzed diazo transfer with *p*-toluenesulfonyl azide were not satisfactory and the product mixture appeared to contain primarily materials in which two *p*-toluenesulfonamide groups had been introduced.[6] Semenuk has studied the diazo transfer process between β-naphthol and *p*-toluenesulfonyl azide under a variety of conditions and found trifluoroethanol to be a favorable solvent.[7] By using this solvent and using *m*-nitrobenzenesulfonyl azide as the diazo transfer reagent, a pure glassy material having the spectral properties expected for a quinonediazide was obtained in 45% yield. The ultraviolet spectrum of this material resembles that of 2-diazonaphthalen-1-one more than it does that of 4-diazonaphthalen-1-one,[8] suggesting that the diazotization had occurred at position 6 of the indole ring to give the 6-diazo-(6H)-indol-7-one.



Photolysis of **8** in methylene chloride with light of hν >400 nm led to the formation of a major new product, isolated in 60% yield as an amorphous glass, in which the proton resonances of the allyl group had been replaced by a series of multiplets corresponding in their spin-spin splitting pattern to the formation of a cyclopropane ring. Direct comparison of this compound with 2 (R = $COCH_3$) which had been previously prepared by Wierenga and his coworkers[10] showed that the two materials were similar but different. The nmr spectral data are given in Table 1. It was noteworthy that compound 9 shows a pronounced temperature dependence of the nmr spectrum. The spectrum is severely broadened at 28° at 90 MgHz and up to 100° at 360 MgHz. Sharp lines (except for some residual broadening of the 4-H and one of the CH_2-N protons) are seen at 110° in DMSO at 360 MgHz. This temperature dependence is attributed to a rotational barrier at the amide group. Some broadening is also evident in the spectrum of 2 (R = $COCH_3$) but the spectrum is sharpened at a lower temperature than is the case for 9. The nonidentity of compound 9 with 2 (R = $COCH_3$) permits confirmation of structure 9 for the photocyclization product. The difference in rotational barriers in the two compounds can be attributed to the stronger vinylogous amide conjugation in 2, which should reduce the rotational barrier of the exocyclic amide bond.

TABLE I. Comparison of Chemical Shifts and Multiplicities for Structures 2 and 9.

	$C-CH_3$	$NCOCH_3$	2-H	4- or 6-H	cyclopropane ring			$-CH_2N$	
					CH_2		CH		
2[a]	1.96 s	2.18 s	6.80 s	6.66 s	1.20 t J≈ 4	1.86 d of d J≈ 4,6	3.02 m	4.04 m $J_{gem} \approx 12$	
9[b]	2.08 s	2.14 s	6.97 s	6.89[c] s	1.33 d of d J = 3,5	1.72 d of d J = 3,7	2.70 d of t[d]	3.90[c] d of d J = 5,11	4.10 d J = 11

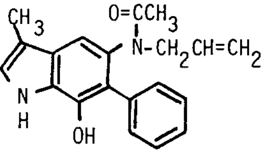
a Recorded in DMSO-d_6 at 70° at 200 MgHz.

b Recorded in DMSO-d_6 at 110° at 360 MgHz.

c Peak shows residual broadening even at 110°.

d Line positions: 2.666, 2.681, 2.687, 2.695, 2.702, 2.716 ppm.

Photolysis of 8 in benzene gave some 9 but the main product was a solvent insertion product, structure 10.



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The nmr spectrum of this compound provided additional support for the conclusion that the diazo transfer reaction had occurred at C-6 of the indole ring. While the chemical shifts of the allyl group were significantly different than in 7, the chemical shift of the indole 3-methyl substituent is essentially unchanged. A phenyl group in the sterically congested 4-position would be expected to have an effect on the chemical shift of the 3-methyl group.

While the regiochemistry of the diazo transfer reaction precludes its use in a direct route to a partial structure of CC-1065, the present work provides the first example of an indole quinonediazide and provides some indication that the isomeric 4-diazo-(4H)-indol-7-one may be a satisfactory precursor of the spiro cyclopropane indolone ring system.

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