Communications to the Editor

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INTRODUCTION OF A FUNCTIONALIZED CARBON CHAIN AT THE 3-POSITION OF 4-METHOXY-2-QUINOLONES VIA PHOTOCHEMICAL 2+2 CYCLOADDITION TO ALKYNES AND THE SYNTHESIS OF (±)-EDULININE[1)]

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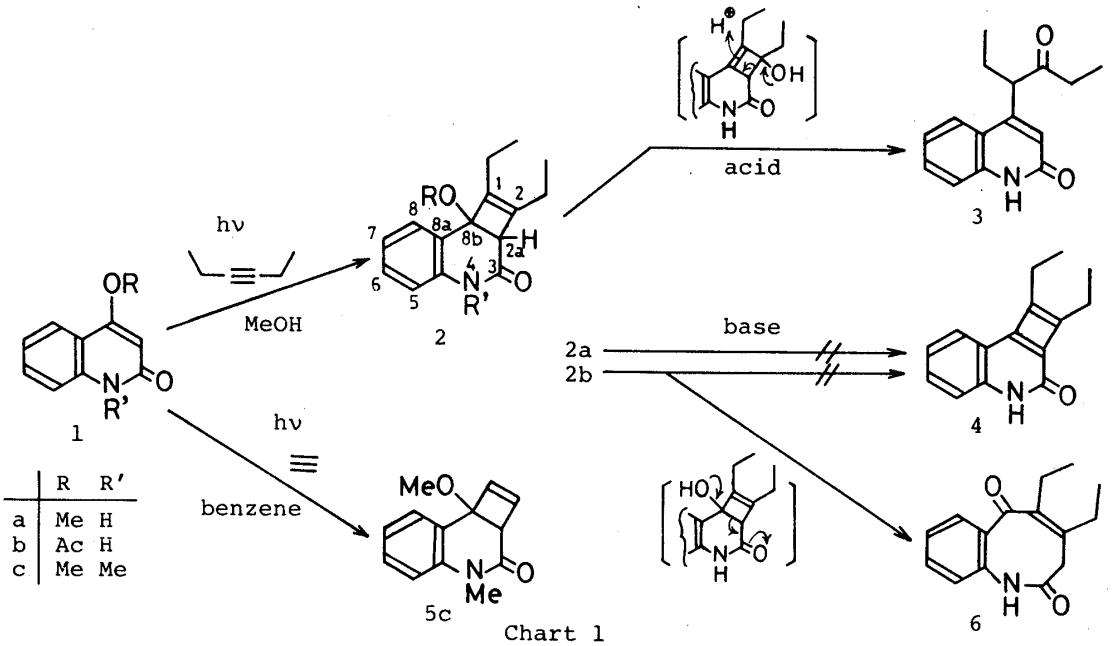
Irradiation of 4-methoxy-2-quinolone or its derivatives in methanol in the presence of mono-substituted ethyne gave the head-to-tail adducts: 1-substituted 2a,8b-dihydrocyclobuta[c]quinolin-3(4H)-one derivatives. A method for fissioning the C_1–C_{8b} bond in the adducts was developed. Based on these findings, the cycloadduct obtained from 4-methoxy-1-methyl-2-quinolone and 2-methyl-3-butyn-2-ol was transformed to (±)-edulinine.

KEYWORDS —— photochemical reaction; 2a,8b-dihydrocyclobuta[c]-quinolin-3(4H)-ones; 2a,8b-dihydrocyclobuta[c]coumarin; 2-methyl-3-butyn-2-ol as isoprenylation reagent; carbon chain introduction to heteroaromatics

As summarized in our recent review,[2)] heteroaromatics involving a β-alkoxy-enone function in their ring system react photochemically with alkenes; and elimination of the alcohol from the adducts provides a convenient synthetic method for cyclobutane-fused heteroaromatics, whose ready accessibility has made possible the extension of the benzocyclobutene method[3,4)] to heteroaromatic compounds. Two characteristic features of the method are high regioselectivity in the first step and facile elimination of the alcohol in the second step. Thus, for example, 4-methoxy-2-quinolone gave exclusively the head-to-tail adducts by photoaddition to mono-substituted olefins, which eliminate methanol by base treatment to give 1-substituted 1,2-dihydrocyclobuta[c]quinolin-3(4H)-ones. In this paper, we describe the photoaddition of 4-methoxy-2-quinolone and some of its related compounds to alkynes and the reactions of the adducts thus formed.

Irradiation[5)] of 4-methoxy-2-quinolone (1a) in methanol containing an excess of 3-hexyne afforded a 2+2 adduct[6)] (2a, mp 140-141°C) in nearly quantitative yield. Though 2a did not react with basic media (NaOMe/MeOH or n-BuLi-DABCO-HMPA), acid treatment (conc. HCl, 85°C) resulted in quantitative formation of the 2-quinolone (3, mp 158-159°C). The recovery of 2a under basic conditions indicates that the elimination of methanol can not occur due to anti-aromaticity of a cyclobutadiene system in the expected product (4). 4-Acetoxy-2-quinolone (1b) also gave the same type of adduct (2b, mp 221-222°C), which also afforded 3 by the acid treatment. In this case, the yield of 2b is low (57%) due to concomitant formation of the dimer[7)] (mp 290°C, 24%) from 1b. Under basic condition (NaOH/MeOH), 2b afforded the

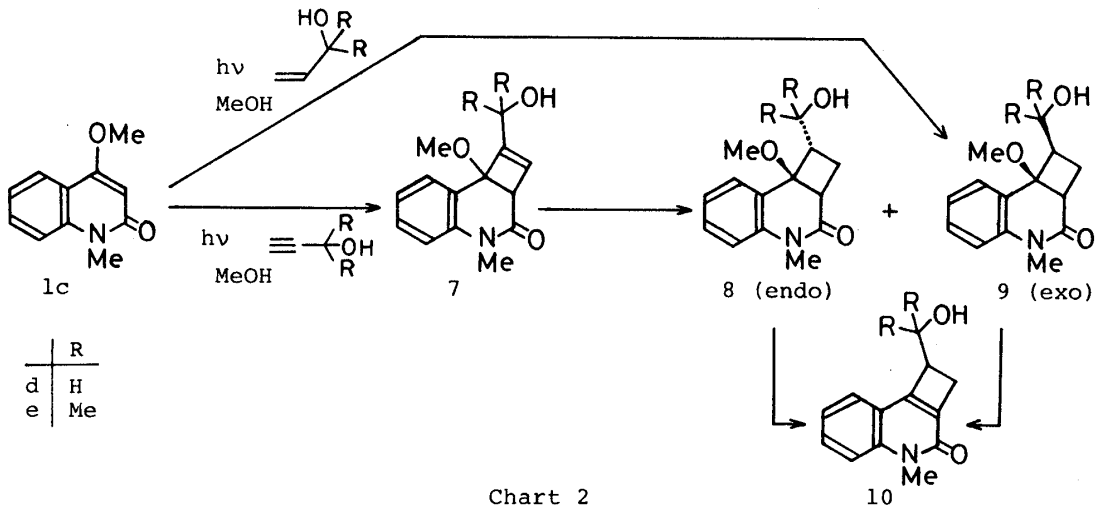


	R	R'
a	Me	H
b	Ac	H
c	Me	Me

Chart 1

benzazocine derivative (6, mp 199.5-200.5°C, 18%) as the only isolable product,[8] and no 4 was detected. The corresponding cycloadduct [5c, mp 125-127°C, δ($CDCl_3$): 3.16 (3H, s), 3.35 (3H, s), 3.78 (1H, bs, C_{2a}-H), 6.04 (1H, dd, J=2.5 and 1.2 Hz), 6.20 (1H, dd, J=2.5 and 1.5 Hz)] was obtained in 36% yield from 4-methoxy-1-methyl-2-quinolone (1c) by irradiation in benzene with bubbling of acetylene.[9]

In order to check regioselectivity of the reaction, we then irradiated 1c in methanol in the presence of propargyl alcohol. As a result, the adduct (7d, mp 135-136°C) was obtained in 71% yield as the sole product. Since the nmr spectra of 7d and its acetate (mp 89-90°C) did not clearly distinguish whether it is a head-to-tail or head-to-head structure,[10] the 7d was reduced by catalytic hydrogenation (Pd/C, room temp.) to the dihydro-derivatives (8d, mp 151-152°C, 55% and 9d, mp 98-99°C, 41%) NMR spectra of both compounds showed their C_{2a}-H signals at δ: 3.21 (8d) and 3.43 (9d) as triplets (8d, J=9.8 Hz and 9d, J=10.5 Hz) and this indicated clearly that 7d has the head-to-tail structure.[11] Both dihydro-derivatives (8d and 9d) afforded the same cyclobutene derivative (10d, mp 145-147°C) in



	R
d	H
e	Me

Chart 2

quantitative yield by treatment with NaOH in methanol (reflux). In a similar manner, the head-to-tail adduct (7e, oil) was formed selectively from 1c and 2-methyl-3-butyn-2-ol in 75% yield. Its structure was again determined by converting it to the dihydro-derivative (9e, mp 92-93°C, 83%).[11] It seems worthy to note that 9d and 9e are the respective sole products obtained from 1c by photoaddition to allyl alcohol or 2-methyl-3-buten-2-ol.[12] These two examples clearly show that the photo-cycloaddition of 4-methoxy-2-quinolone derivatives (1a-1c) to mono-substituted acetylenes proceeds regioselectively to give only the head-to-tail adducts, the same as in their cycloaddition to mono-substituted olefins.[2]

During the studies on the reaction of the adducts obtained from 4-methoxy-2-quinolones (1a-1c) and alkynes, a novel method for the introduction of a functionalized carbon chain into the 3-position of the 2-quinolone ring was disclosed. Thus, the adduct (2a) was treated by m-CPBA in $CHCl_3$ (room temp.) to give the epoxide (11, mp 195-196°C) in 93% yield. Refluxing of 11 in 1% NaOH/MeOH gave 86% yield of the 4-methoxy-2-quinolone (12, mp 140.5-142°C) as the sole product. This selective C_1-C_{8b} bond fission may proceed by the mechanism shown by the arrow symbols depicted in formula 11. Utility of this novel alkylation of 1 for 2-quinolone alkaloid synthesis was demonstrated by the following three-step synthesis of (±)-edulinine. The epoxides (13, mp 142-143.5°C, 53% and 14, mp 97-98.5°C, 15%) obtained from 7e by the peracid oxidation were separately treated by a base as in the case of 11 to 12 to give the α-hydroxy-ketone (15, mp 112-113°C, quant. from 13 and 41% from 14), which by reduction with $NaBH_4$ in methanol gave (±)-edulinine[13] [16, mp 145-146°C, δ($CDCl_3$): 1.28 (6H, s), 2.62 (1H, dd, J=13 2n4 9 Hz), 3.07 (1H, dd, J=13 and 2.2 Hz), 3.52 (1H, dd, J=9 and 2.2 Hz), 3.66 and 3.88 (2 x CH_3, each s)] in quantitative yield.

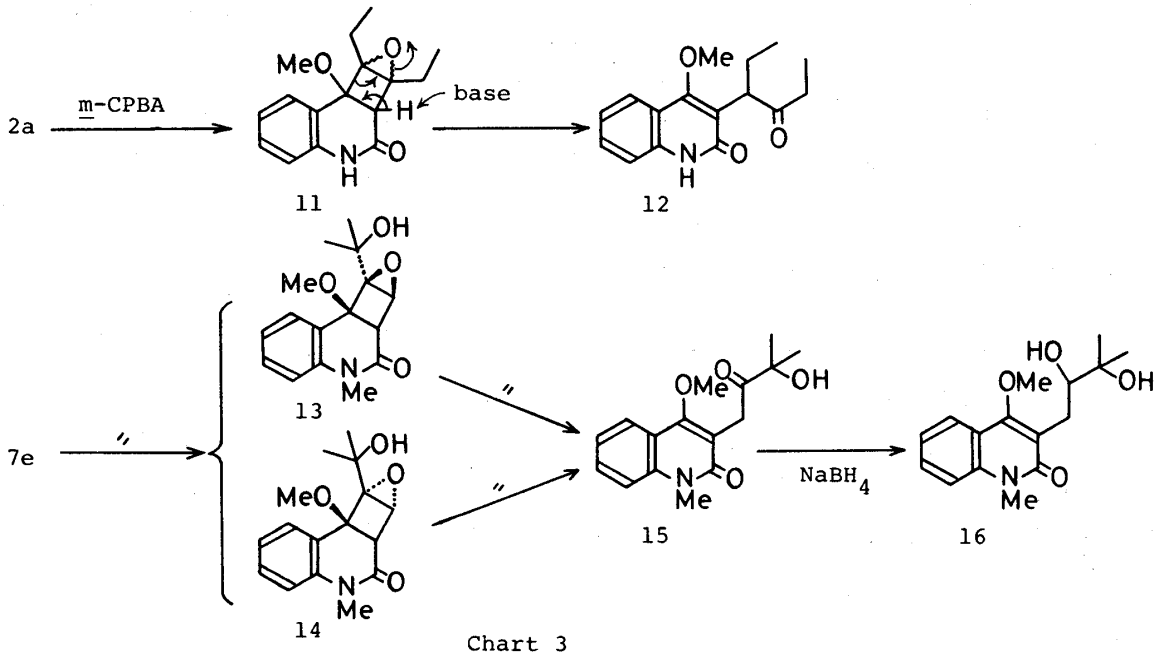


Chart 3

4-Methoxycoumarin (17) also gave the cycloadduct (18, oil, 46%) with 3-hexyne.[14] This indicates that the addition of alkynes to heteroaromatics having a β-alkoxy-enone function in their ring system is a common phenomenon, and hence, introduction of a carbon chain at the 3-position of these ring systems by the

above route should have wide applicability.[15]

REFERENCES AND NOTES

1) Part XIII of "Cycloadditions in Syntheses." For Part XII, see: C. Kaneko, Y. Momose, and T. Naito, Chemistry Letters, 1982, 1361.

2) C. Kaneko and T. Naito, Heterocycles, 19, 2183 (1982).

3) W. Oppolzer, Synthesis, 1978, 793.

4) T. Kametani and K. Fukumoto, Heterocycles, 3, 29 (1975).

5) All irradiations were carried out at room temp. with a Toshiba 400P high-pressure mercury lamp using a Pyrex filter. The irradiation was done using a 5-10 mM solution of 1 in methanol containing a 20-100 mol equivalent of substituted acetylenes under argon. For acetylene, the irradiation was done under its bubbling.

6) The structure of all compounds was verified by elemental analyses, and by mass and other spectra (NMR, UV, IR).

7) O. Buchardt, Acta Chem. Scand., 18, 1389 (1964); M. Ishikawa, S. Yamada, H. Hotta, and C. Kaneko, Chem. Pharm. Bull., 14, 1102 (1966).

8) Similar retro-aldol type ring opening reactions have been observed for the adducts obtained from 1b and olefins. See: T. Naito and C. Kaneko, Chem. Pharm. Bull., 28, 3150 (1980).

9) The low yield of the adduct (5c) is due to low solubility of acetylene in benzene. The use of methanol as the irradiation solvent under the same condition further lowered the yield of 5c.

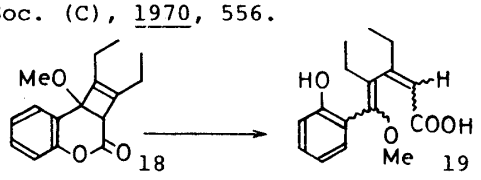
10) The C_{2a}-H signals of 7d and its acetate appeared as broad singlets at δ: 3.73 and 3.72, respectively. These signals are coupled with both olefinic protons (J=1.5 Hz) and the protons on CH_2OH (J=2.5 Hz). Similar long-range coupling is observed in the related 1-methylcyclobutene derivatives. See: D.G. Farnum, M.A.T. Heybey, and B. Webster, J. Am. Chem. Soc., 86, 673 (1964).

11) The stereochemistry of 1,2-dihydro-derivatives was tentatively deduced from the chemical shift of C_1-$C\underline{H}_2$-OH or C_1-$C(C\underline{H}_3)_2$-OH signals, based on the reasonable assumption that in the endo isomer (where the phenyl ring and the 1-substituent are cis to each other on the cyclobutane ring) these protons are shielded by the phenyl ring, while in the exo-isomer no such shielding exists. For example, the CH_2 signal of the acetate (mp 123-124°C) of 8d appeared at a higher region (δ: 3.80, d, J=6.8 Hz) than that (δ: 4.21, dd, J=11 and 7.2 Hz, and 4.50, dd, J=11 and 6.8 Hz) of the acetate (oil) of 9d.

12) Allyl alcohol or its 1-alkyl derivatives add to 1a-1c stereoselectively to give only the exo-isomer (9).

13) a) T.P. Toube, J.W. Murphy, and A.P. Cross, Tetrahedron, 23, 2061 (1967); b) D.R. Boyd and M.F. Grundon, J. Chem. Soc. (C), 1970, 556.

14) The compound (18) is hydrolysed slowly to 19 upon standing in an open vessel.



15) Similar isoprenylation of 2-quinolones and 2-pyridones via their photoaddition to 2-methyl-3-buten-2-ol was recently disclosed. See: T. Naito, Y. Momose, and C. Kaneko, Chem. Pharm. Bull., 30, 1531 (1982).

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