Tetrahedron Letters, Vol.22, No.30, pp 2893 - 2894, 1981
Printed in Great Britain

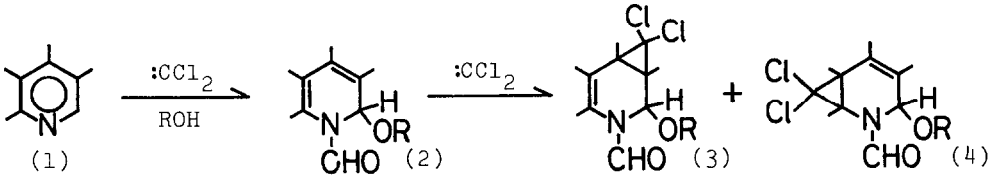
0040-4039/81/302893-02$02.00/0

FORMATION OF 1,1-DIALKOXY-1,2-DIHYDROCYCLOBUTA[b]QUINOLINE FROM A 1',2'-DIHYDROSPIRO[CYCLOPROPANE-1,2'-QUINOLINE] DERIVATIVE

Yoshiki Hamada, Michiharu Sugiura, and Minoru Hirota*
Pharmaceutical Faculty, Meijo University, Tempaku-ku, Nagoya 468, Japan
* Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Hodogaya-ku, Yokohama 240, Japan

1,1-Dialkoxy-1,2-dihydrocyclobuta[b]quinolines were obtained in good yields starting from 2-methylquinoline, the key intermediate being 2,2-dichloro-1'-formyl-1',2'-dihydrospiro[cyclopropane-1,2'-quinoline].

In the series of investigations towards the synthetic applications of pseudo bases derived from pyridinoid aza-aromatics,[1] the authors have carried out the reactions of dichlorocarbene on various aza-aromatics.

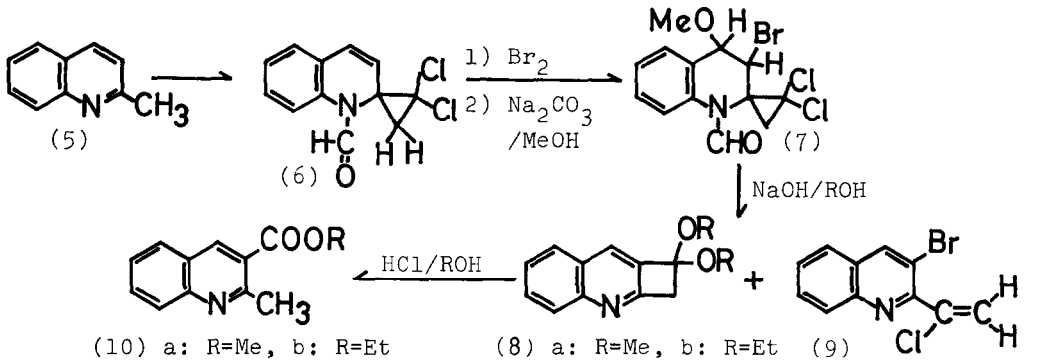


(1) (2) (3) (4)

In general, tetrahydrocyclopropa[b] or [c]pyridine derivatives 3 and/or 4 were obtained probably via the pseudo base intermediate 2 when they were reacted with dichlorocarbene. The pseudo base 2 was isolated in some reactions.

2-Methylquinoline behaves rather differently from other aza-aromatics without ortho-methyl group. In this publication, we intend to report the reaction of 2-methylquinoline (5) towards dichlorocarbene with special interest on the formation of cyclobuta[b]quinoline derivative (8). The pseudo base, 2,2-dichloro-1'-formyl-1',2'-dihydrospiro[cyclopropane-1,2'-quinoline] (6),[2] was dissolved in methanol and reacted with a slightly excess amount of molecular bromine at room temperature. Then the reaction mixture was neutralized by saturated sodium carbonate solution, diluted with water, and extracted by methylene chloride. The purification by column chromatography and successive recrystallization from benzene/hexane (1:1) gave 3-bromo-2,2-dichloro-1'-formyl-1',2',3',4'-tetrahydrospiro[cyclopropane-1,2'-quinoline] (7) as colorless crystals in 89% yield. Mp. 132-133°C. Found: C, 42.93; H, 3.25; N, 3.70%. Calcd for $C_{13}H_{12}NO_2Cl_2Br$: C, 42.76; H, 3.31; N, 3.84%. MS(70 eV), m/e 284[$(M-Br)^+$].

The compound 7 was dissolved in methanol and 50% aqueous sodium hydroxide solution was added dropwise at room temperature with efficient stirring during 0.5 h. Then the whole mixture was poured into a large excess of water and



extracted by dichloromethane. The crude mixture of products was separated by column chromatography on silica gel to give 1,1-dimethoxy-1,2-dihydrocyclobuta-[b]quinoline (8a) in 79% yield.[3] Very slight but detectable amount of 9 was obtained in addition to the main product 8a. Similar treatment of 7 in ethanol gave 8b and 9 in 68 and 8% yields, respectively. 8a: Bp. 120-122°C/0.08mmHg. Found: C, 72.70; H, 5.95; N, 6.63%. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51%. ^{1}H-NMR, ($CDCl_3$) = 3.48(6H, s, CH_3O), 3.74(2H, s, CH_2), 7.88(1H, s, 8-H), 7.30-8.20(4H, m, arom-H). 8b: Bp. 125-130°C/0.08mmHg. Found: C, 74.30; H, 7.11; N, 5.90%. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76%. ^{1}H-NMR, ($CDCl_3$) = 1.28(6H, t, CH_3), 3.76(4H, q, CH_2O), 3.76(2H, s, CH_2), 7.86(1H, s, 8-H), 7.30-8.20(4H, m, arom-H).

It is generally accepted that the cleavage of 1,1-dichloropropane ring is feasible to occur at the bond opposite to the dichlorinated carbon atom.[4] In the above experiments, however, the predominant path to give 8 proceeds via the bond fission adjacent to the dichlorinated carbon atom, the opposite bond fission occuring only subsidiary to give 9 as a minor product.

The structure of 8 was proved more confidently by deriving them to the corresponding 2-methylquinoline-3-carboxylic esters (10a and 10b). Thus, 8 was heated with aqueous methanol solution of hydrogen chloride under reflux for 1 h, giving 10. It is remarkable that the alkoxyl moiety in 10 derives from the original alkoxyl group of 8. The crossover experiment using 8a and ethanol and vice versa gave 10a(62%) and 10b(65%), respectively, as the main products. The cross products obtained (in 14 and 12% yields) as the minor products probably come from the acid-catalyzed alkoxyl exchange. Both 10a and 10b further transformed to 3-hydroxymethyl-2-methylquinoline by $NaBH_4$ reduction and identified by the coincidence with the reported spectral data.

References 1) Y. Hamada, M. Sugiura, and M. Hirota, Yakugaku Zasshi, 98, 1361 (1978); Chem. Pharm. Bull., 27, 1518 (1979). 2) Y. Hamada and M. Sugiura, Yakugaku Zasshi, 100, 168 (1980). 3) 1,2-Dihydrocyclobuta[b] quinoline itself has been reported by J. H. Markgraf and co-workers. [J. Org. Chem., 34, 4131 (1969).] 4) T. Hiyama and H. Nozaki, Yukigosei Kagaku Kyokai Shi, 35 979 (1977)

(Received in Japan 20 April 1981)