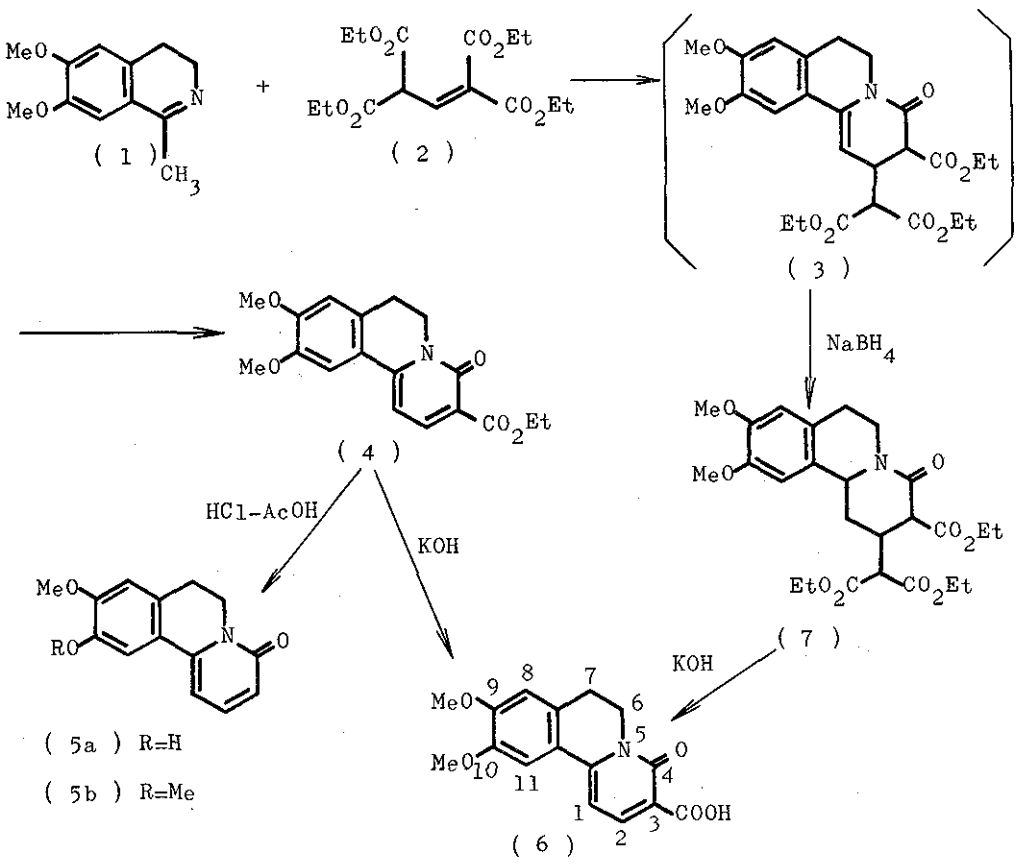
A FACILE FORMATION OF BENZO[a]QUINOLIZIN-4-ONES

Tetsuji Kametani,* Hirofumi Terasawa, Masataka Ihara
and Keiichiro Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

Reaction of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (1) with diethyl α,γ-diethoxycarbonylglutaconate (2) in ethanol, followed by silica gel chromatography, gave 3-ethoxycarbonyl-6,7-dihydro-9,10-dimethoxybenzo[a]quinolizin-4-one (4). On the other hand, the above same reaction, followed by reduction with sodium borohydride, yielded 3-ethoxycarbonyl-2-diethoxycarbonylmethyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[a]quinolizin-4-one (7). Hydrolysis of 4 and 7 with ethanolic potassium hydroxide furnished the same acid (6).

Recently we have reported new synthetic methods for benzo[a]quinolizines from 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline by application of its enamine character.[1] In order to find out the general methods for obtaining 2,3-disubstituted benzo[a]quinolizines for the total synthesis of natural products, we further studied the annelation of the isoquinoline with unsaturated esters and here wish to report one-step synthesis of benzo[a]quinolizin-4-ones.

3,4-Dihydro-6,7-dimethoxy-1-methylisoquinoline[2] (1) was stirred for 5 h with diethyl α,γ-diethoxycarbonylglutaconate[3] (2) at room temperature in ethanol. Purification of the product by silica gel chromatography gave, in 75 % yield, 3-ethoxycarbonyl-6,7-dihydro-9,10-dimethoxybenzo[a]quinolizin-4-one (4), mp 189 - 190°, m/e 329 (M^+), together with diethyl malonate. This product (4) showed carbonyl absorptions at 1720, 1685, 1650 cm^{-1} in its ir spectrum and the nmr spectrum revealed the following resonances; δ 1.37 (3H, t, J = 7 Hz, $COOCH_2C\underline{H}_3$), 3.97 (6H, s, OCH_3), 4.35 (2H, q, J = 7 Hz, $COOC\underline{H}_2CH_3$), 6.54 (1H, d, J = 8 Hz, 1-H), 6.73 (1H, s, 8-H), 7.16 (1H, s, 11-H) and 8.08 (1H, d, J = 8 Hz, 2-H). It is probable that the Michael reaction of 1 with 2, followed by cyclization, would have yielded an enamide (3), which was then subjected to retro Michael reaction to give 4 and diethyl malonate. Hydrolysis of 4 with aqueous ethanolic potassium hydroxide for 6 h at 50° gave, in 85 % yield, the corresponding carboxylic acid (6), mp > 270° (from methanol), which showed carbonyl absorptions at 1740, 1620 cm^{-1} in ir (KBr) spectrum and the following signals; δ 3.28 (2H, t, J = 7 Hz, $C\underline{H}_2$-CH_2-N<), 4.12 (6H, s, OCH_3), 4.73 (2H, t, J = 7 Hz, -$CH_2C\underline{H}_2$-N), 7.06 (1H, s, 8-H), 7.57 (1H, s, 11-H), 7.80 (1H, d, J = 8.5 Hz, 1-H) and 8.80 (1H, d, J = 8.5 Hz, 2-H) in nmr spectrum (CF_3CO_2H). Refluxing 4 with a mixture (1 : 1 v/v) of concentrated hydrochloric acid and acetic acid for 20 h afforded, in 65 % yield, a phenolic compound (5a) as the hydrochloride, mp 235 - 238°, which was assigned to 6,7-dihydro-10-hydroxy-9-methoxybenzo[a]-quinolizin-4-one since demethylation accompanied with deethoxycarbonylation would occur preferentially at the 10-methoxyl group rather than the 9-methoxyl group because of its electronic factor.[4] This


MeO
MeO
(1)
CH3
+
EtO2C
CO2Et
EtO2C
CO2Et
(2)
(3)
(4)
NaBH4
(7)
HCl-AcOH
KOH
KOH
RO
(5a) R=H
(5b) R=Me
COOH
(6)

product showed carbonyl absorption at 1640 cm^{-1} in ir (KBr) spectrum and the following resonances; δ 3.20 (2H, broad t, J = 7 Hz, $-C\underline{H}_2-CH_2-N$), 4.08 (3H, s, OCH_3), 4.65 (2H, broad t, J = 7 Hz, $-CH_2C\underline{H}_2-N$), 7.00 (1H, s, 8-H), 7.27 (1H, d, J = 8 Hz, 1-H or 3-H), 7.57 (1H, s, 11-H), 7.63 (1H, d, J = 8 Hz, 1-H or 3-H), and 8.18 (1H, t, J = 8 Hz, 2-H) in nmr spectrum (CF_3CO_2H).

Methylation of 5a with diazomethane gave (5b), mp 173 - 174° [lit.,[5] mp 172 - 173°], the spectroscopic data of which were superimposable upon those of an authentic sample.

In order to prevent the above retro Michael reaction, the reaction product was reduced with sodium borohydride. Namely, after stirring a mixture of 1 and 2 in a similar manner as mentioned above, sodium borohydride was added to the reaction mixture at room temperature. A usual work-up, followed by purification of the reaction product by silica gel chromatography, gave in 60 % yield the triester (7) as a colorless syrup, m/e 491 (M^+), which showed carbonyl band at 1725, 1640 cm^{-1} in ir spectrum and the signals, δ 1.24 (3H, t, J = 7 Hz, $COOCH_2C\underline{H}_3$), 1.28 (6H, t, J = 7 Hz, $COOCH_2C\underline{H}_3$), 3.73 (6H, s, OCH_3), 4.12 (2H, q, J = 7 Hz, $COOC\underline{H}_2CH_3$), 4.15 (4H, q, J = 7 Hz, $COOC\underline{H}_2CH_3$), 6.45 (1H, s, 8-H), and 6.53 (1H, s, 11-H) in nmr spectrum but its stereochemistry was unclear. Saponification of 7 with aqueous ethanolic potassium hydroxide at 50° for 6 h gave the carboxylic acid (6) in 40 % yield, which was identical with the sample obtained from 4 and would have been formed by retro Michael reaction accompanied with dehydrogenation.

Application of this new annelation to alkaloid synthesis is under investigation.

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