SYNTHESIS OF PYRIDO[2,1-a]ISOINDOL-6(2H)-ONE AND ITS ANALOGS

Yoshihito Abe, Akio Ohsawa and Hiroshi Igeta*
School of Pharmaceutical Sciences, Showa University,
Shinagawa-ku, Tokyo 142, Japan

Abstract--- Treatment of o-(2-pyridyl)benzaldiacetate (1a) with HCl afforded pyrido[2,1-a]isoindol-6(2H)-one (3a). 6-Hydroxypyrido-[2,1-a]isoindolium hydrochloride (5) was suggested to be an intermediate. Isoindolo[2,1-a]quinolin-11(5H)-one (3b) and isoindolo[1,2-a]isoquinolin-8(12bH)-one (3c) were obtained in a similar way. Enol isomers (e.g. 7) of 3a-c were not detected by ^{1}HNMR and ^{13}CNMR spectrum.

In connection with our study[1] on synthesis of aminoindolizine derivatives, we needed to prepare o-(2-pyridyl)benzaldehyde. Thus, we attempted hydrolysis of o-(2-pyridyl)benzaldiacetate with HCl and found that an unexpected cyclized product was formed instead of the aldehyde.

o-(α-Azaaryl)benzaldiacetates (1a-c) were prepared from 2-bromopyridine (2a), 2-chloroquinoline (2b), and 1-chloroisoquinoline (2c) by the reaction sequence shown in Chart 1.

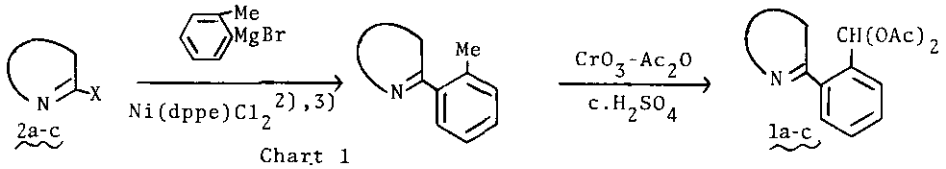


Chart 1

A solution of 1a in 10% HCl was heated at 80°C for 1 h and the reaction mixture was neutralized by $NaHCO_3$ to give a somewhat air-sensitive compound (3a) of mp 99-100°C in 54% yield [^{1}HNMR(δ):2.16(2H,m,2-H$_2$),5.21(1H,m,3-H),5.88(1H,td,1-H),7.08(1H,td,4-H),7.3-7.7(3H,m,8,9,10-H),7.88(1H,m,6-H),$J_{1,2}$=7,$J_{1,3}$=2,$J_{2,3}$=7.5,$J_{2,4}$=7Hz. IR(KBr):1700,1695(CO). MS m/e:183(M^+),182(M^+-H,base peak),154(M^+-HCO)]. Catalytic reduction of 3a afforded a tetrahydro compound (4). Its ^{1}HNMR spectrum [2.94(1H,

ddd,4ax-H),4.25(1H,dd,10b-H),4.47(1H,dm,4eq-H),$J_{4ax,4eq}$=12,$J_{4ax,5eq}$=2,$J_{4ax,5ax}$=12, $J_{1ax,10b}$=12,$J_{1eq,10b}$=2Hz] suggested that 4 contains a piperidine ring. A solution of 3a in 10% HCl was heated at 80°C to give a hydrochloride (5) of mp 180-185°C (decomposition). Its ^{1}HNMR spectrum (D_2O) indicated the presence of pyridinium ring [8.37(1H,d,1-H),8.62(1H,dd,2-H),9.07(1H,d,4-H),$J_{1,2}$=8,$J_{2,3}$=8,$J_{3,4}$=6Hz], and the ^{13}CNMR spectrum (D_2O) showed $N^+CH(OH)$- at 93.2ppm. Neutralization of 5 by $NaHCO_3$ afforded 3a in 52% yield. On the basis of these observations, 3a and 5 are reasonably assigned pyrido[2,1-a]isoindol-6(2H)-one and 6-hydroxypyrido[2,1-a]-isoindolium hydrochloride. When a solution of 1b in 10% HCl was heated at 50°C for 2 h and the reaction mixture was neutralized, isoindolo[2,1-a]quinolin-11(5H)-one (3b) of mp 145-146°C was obtained in 14% yield. Its ^{13}CNMR spectrum indicated that the structure of 3b was similar to that of 3a [^{1}HNMR(δ):3.79(2H, d,5-H_2),6.06(1H,t,6-H),7.0-8.0(7H,m,2,3,4,7,8,9,10-H),9.00(1H,d,1-H),$J_{1,2}$=8, $J_{5,6}$=3Hz. IR(KBr):1700,1690(CO). MS m/e:233(M^+),232(M^+-H,base peak),204(M^+-HCO)].

A solution of 1c in 10% HCl was heated at 80°C for 1 h and the reaction mixture was neutralized to give isoindolo[1,2-a]isoquinolin-8(12bH)-one (3c) of mp 114-115°C in 60% yield. Its mass spectrum showed a similar pattern to that of 3b [^{1}HNMR(δ):5.85(1H,s,12b-H),6.21(1H,d,5-H),6.8-8.0(9H,m,1,2,3,6,9,10,11,12-H),$J_{5,6}$=8Hz. IR(KBr):1710,1705(CO). MS m/e:233(M^+),232(M^+-H,base peak),204(M^+-HCO)].

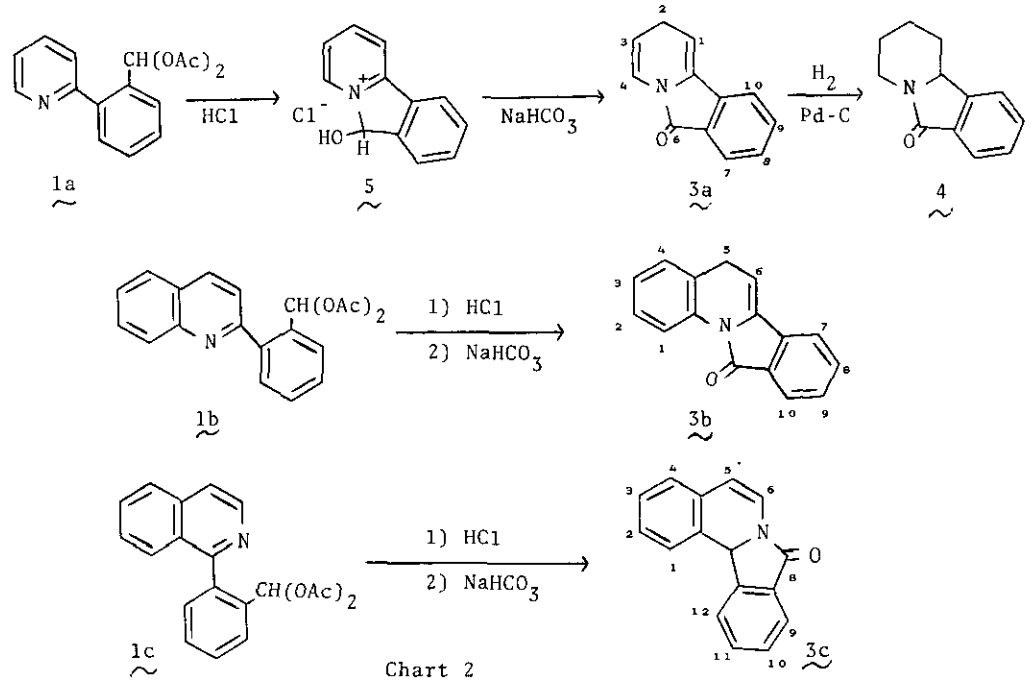
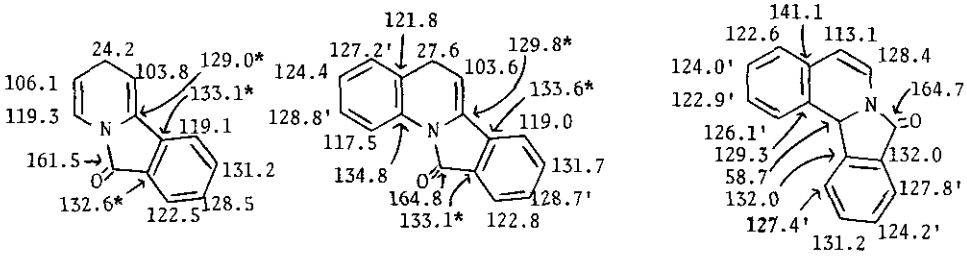


Chart 2

^{13}CNMR spectrum data (assignment bearing the same superscript in any one spectrum may be interchanged.)



The formation of 3a may be explained by the course shown in Chart 3. An aldehyde (6), formed by hydrolysis of 1a, cyclizes to give 5. Neutralization of the salt (5) leads to the elimination of HCl to give the hydroxyl compound (7), followed by ketonization to afford the stable isomer (3a).

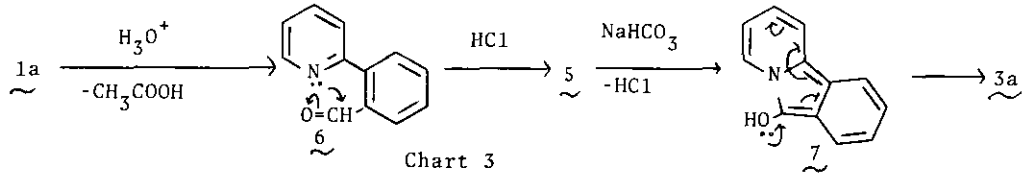


Chart 3

Enol isomers (e.g. 7) were assumed to be intermediates of the reaction from 1 to 3, but signals to be assigned to these were not indicated by both ^{1}H and ^{13}CNMR spectra of 3a-c. It was assumed that the keto forms (3a-c) are more stable than the enol forms since the fomer have stable benzene rings.

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