

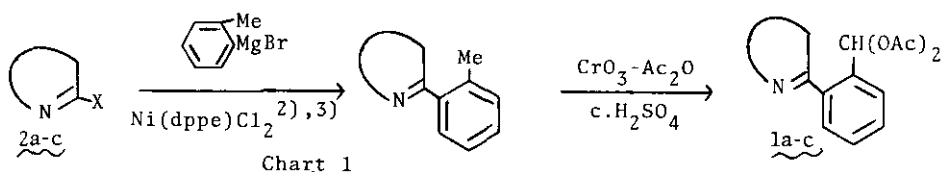
SYNTHESIS OF PYRIDO[2,1-*a*]ISOINDOL-6(2H)-ONE
AND ITS ANALOGS

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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 ¹HNMR and ¹³CNMR spectrum.

In connection with our study¹⁾ 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.

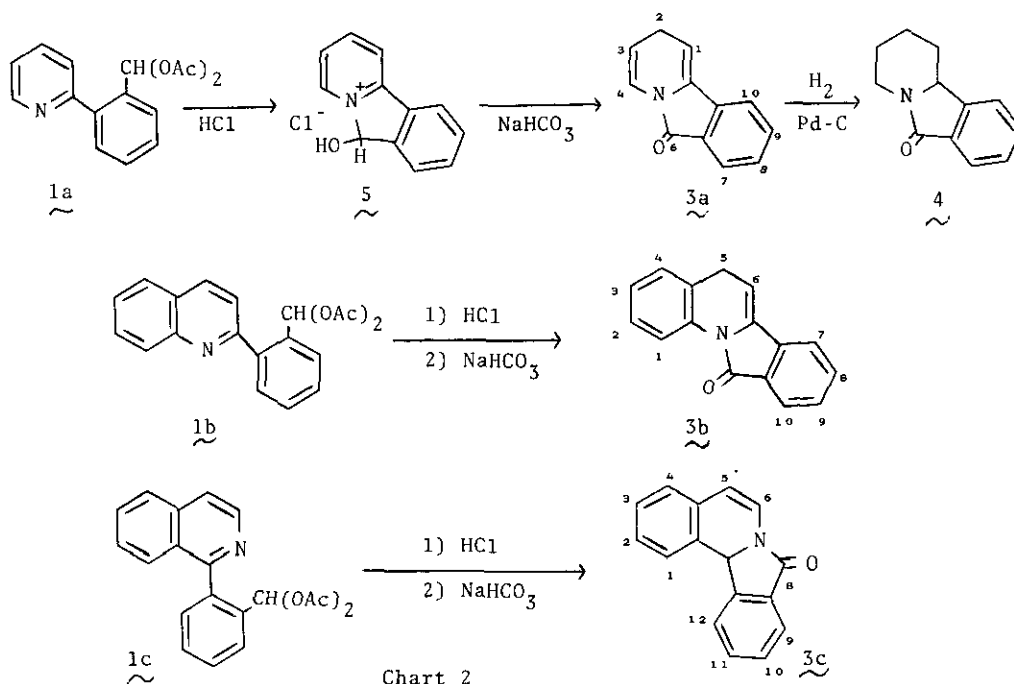
o-(α -Azaaryl)benzaldiacetates (**1a-c**) were prepared from 2-bromopyridine (**2a**), 2-chloroquinoline (**2b**), and 1-chloroisoquinoline (**2c**) by the reaction sequence shown in Chart 1.



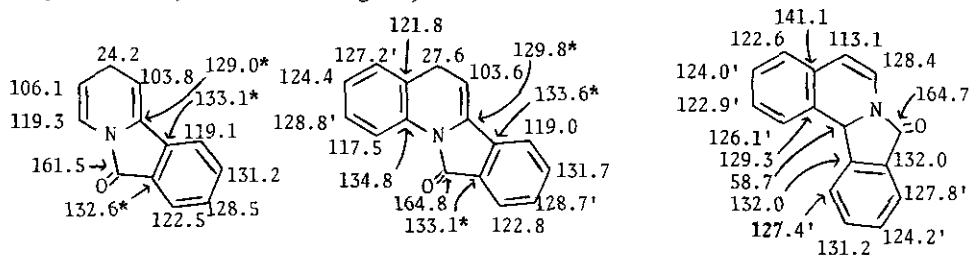
A solution of **1a** in 10% HCl was heated at 80°C for 1 h and the reaction mixture was neutralized by NaHCO₃ to give a somewhat air-sensitive compound (**3a**) of mp 99-100°C in 54% yield [¹HNMR(δ): 2.16(2H, m, 2-H₂), 5.21(1H, m, 3-H), 5.88(1H, td, 1-H), 7.08(1H, td, 4-H), 7.3-7.7(3H, m, 8, 9, 10-H), 7.88(1H, m, 6-H), J_{1,2}=7, J_{1,3}=2, J_{2,3}=7.5, J_{2,4}=7 Hz. 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 ¹HNMR spectrum [2.94(1H,

ddd, 4ax-H), 4.25 (1H, dd, 10b-H), 4.47 (1H, dm, 4eq-H), $J_{4ax,4eq}=12, J_{4ax,5eq}=2, J_{4ax,5ax}=12, J_{1ax,10b}=12, J_{1eq,10b}=2$ Hz] 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 ^1H NMR 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), $J_{1,2}=8, J_{2,3}=8, J_{3,4}=6$ Hz], and the ^{13}C NMR spectrum (D_2O) showed $\text{N}^+\text{CH}(\text{OH})^-$ at 93.2 ppm. 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}C NMR spectrum indicated that the structure of 3b was similar to that of 3a [^1H NMR(δ): 3.79 (2H, d, 5-H₂), 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), $J_{1,2}=8, J_{5,6}=3$ Hz]. IR (KBr): 1700, 1690 (CO). MS m/e: 233 (M^+), 232 (M^+-H , base peak), 204 (M^+-HCO).

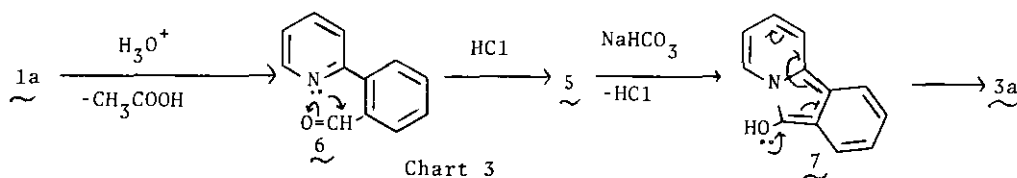
A solution of 1c in 10% HCl was heated at 80°C for 1 h and the reaction mixture was neutralized to give isoindolo[1,2-a]isoquinolin-8(12bH)-one (3c) of mp 114-115°C in 60% yield. Its mass spectrum showed a similar pattern to that of 3b [^1H NMR(δ): 5.85 (1H, s, 12b-H), 6.21 (1H, d, 5-H), 6.8-8.0 (9H,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



^{13}C NMR 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).



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 ^1H and ^{13}C NMR spectra of 3a-c. It was assumed that the keto forms (3a-c) are more stable than the enol forms since the former have stable benzene rings.

Acknowledgement This work was supported in part by a Grant-in-Aid (No. 56570729) for Scientific Research from the Ministry of Education, Science and Culture of Japan, which is gratefully acknowledged.

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Received, 21th September, 1981