QUINOLIZIDINES. IX.[1] AN IMPROVED PROCEDURE FOR THE SYNTHESIS OF INDOLO[2,3-a]QUINOLIZIDINE FROM 3-(2-PIPERIDINOETHYL)INDOLE

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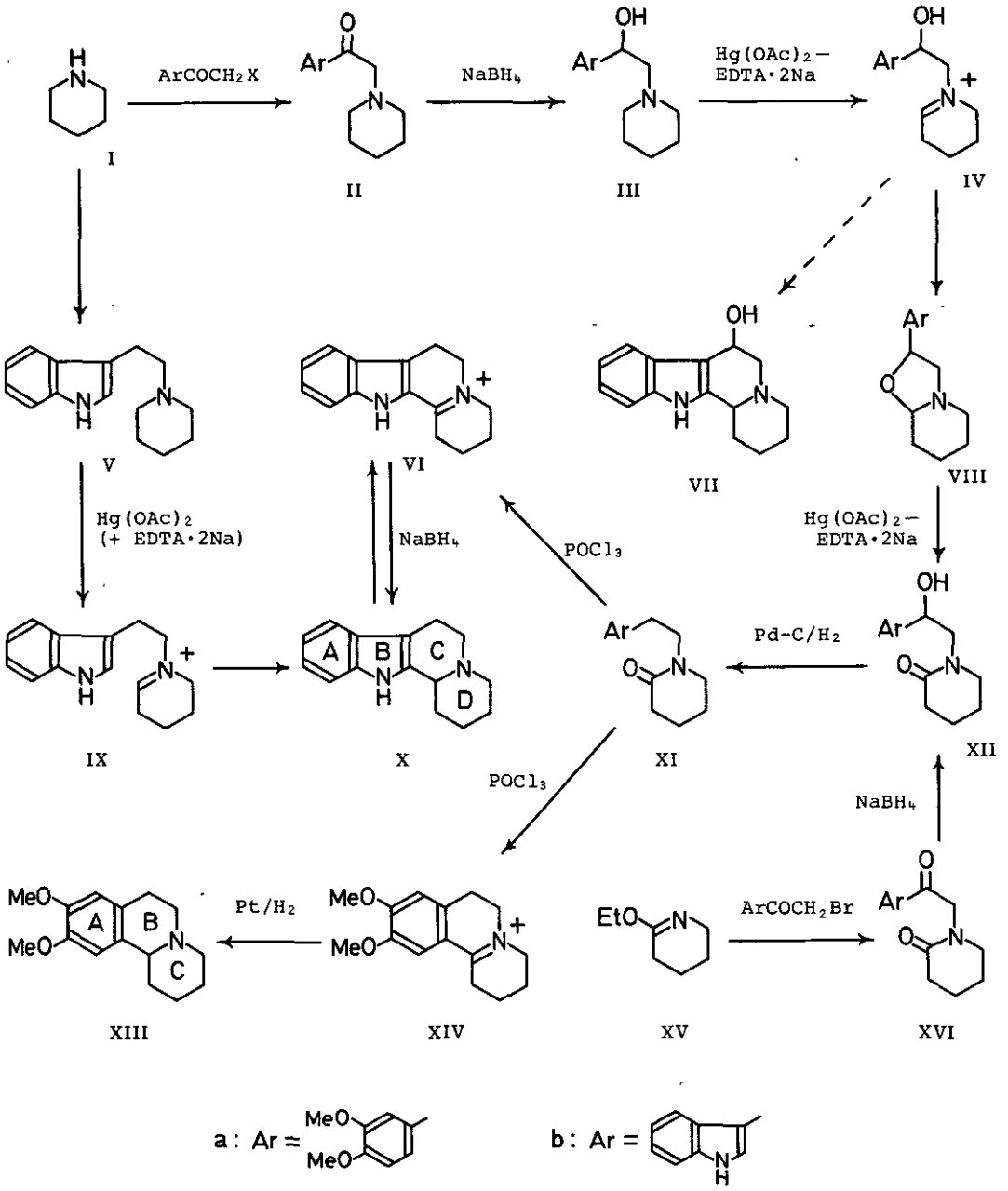
Abstract—— The procedure and yield of the oxidative cyclization of 3-(2-piperidinoethyl)indole (V) to produce indolo[2,3-a]quinolizidine (X) have been improved by the use of 3 molar equivalents of $Hg(OAc)_2$–edetate disodium in boiling aqueous EtOH for 3 h. Similar oxidation of the piperidinoethanol IIIb in boiling 1% aqueous AcOH failed to give the expected lactam alcohol XIIb, an alternative intermediate for the synthesis of X.

The tricycle XIII represents the parent carbon skeleton common to the benzoquinolizidine moiety of most of the ipecac alkaloids and many of the Alangium alkaloids.[2] We have already opened two synthetic routes to XIII; one from piperidine (I) through IIa, IIIa, (IVa, VIIIa), XIIa, XIa, and XIV ("oxazolidine–lactam route"),[3] and the other from the lactim ether XV through XVIa, XIIa, XIa, and XIV ("lactim ether route").[4] Both routes have proved widely applicable to synthesis of benzo[a]-quinolizidines (type XIII) carrying substituents in ring A and/or ring C,[5] and good illustrations of their utility may be found in our syntheses of several Alangium alkaloids.[1,2,6] Structurally analogous to XIII is the tetracycle X, which is the simplest among a number of indoloquinolizidine alkaloids.[7] We have found that the above "lactim ether route" also worked well for synthesizing this parent framework (X) from XV through XVIb, XIIb, XIb, and VI.[8,9] The present paper describes the results of our further efforts to obtain X via an alternative route.

We first tried to assess the applicability of the above "oxazolidine–lactam route" to the indoloquinolizidine series. Conversion of I into the piperidinoethanol IIIb through the piperidinoketone IIb was accomplished according to the literature, but 3-bromoacetylindole for the first step[10] was replaced by 3-chloroacetylindole and catalytic reduction for the second step,[11] by $NaBH_4$ reduction. On treatment with 2.5 or 5 equivalent moles of $Hg(OAc)_2$–edetate disodium (EDTA·2Na) in boiling 1% aqueous AcOH under the previously reported standard conditions,[3] however, IIIb failed to give the expected lactam alcohol XIIb, an intermediate for our previous synthesis[8] of X via the "lactim ether route". This failure suggested that electrophilic cyclization of the iminium group carbon with the indole moiety in IVb



to yield VII might be more favored than the desired cyclization with the benzylic hydroxyl group to form the oxazolidine VIIIb. However, isolation of VII from the same oxidation products or from their $NaBH_4$ reduction products was unsuccessful. In consideration of the instability observed by us[8] for the benzylic hydroxyl group in XIIb and hence in VII, we abandoned the "oxazolidine–lactam route" in the indoloquinolizidine series and renewed our interest in the "oxidative cyclization route" (I ⟶ V ⟶

TABLE 1. Conversion of Amine V into Tetracycle X by Oxidative Cyclization

Entry[a]	Solvent[b]	Amount of reagent (Molar equivalent)[c]		Reaction conditions		Product X Yield (%)[d]	Recovery of V (%)[d,e]
		$Hg(OAc)_2$	EDTA[f]	Temp. (°C)	Time (h)		
1	A	5	5	110	1.5	80	—
2	A	2.5	2.5	110	1.5	58	—
3	B	10	0	100	1	3	25
4	C	5.6	5.6	80	1.3	31	40
5	D	6	6	80	7	71	—
6	D	9	9	reflux	3	84	—
7	D	10	0	reflux	3	11	—
8	D	6	6	reflux	3	83	—
9	D	5	5	reflux	3	86	—
10	D	4	4	reflux	3	85	—
11	D	3	3	reflux	3	85	—
12	D	2.5	2.5	reflux	3	81	5
13	D	2	2	reflux	3	75	13
14	D	1.75	1.75	reflux	3	68	19
15	D	1.5	1.5	reflux	3	60	27
16	D	1	1	reflux	3	38	37

a) In all runs, 457 mg (2 mmol) of the amine V was subjected to oxidative cyclization followed by reduction with $NaBH_4$ (757 mg, 20 mmol). For details of the reaction conditions, see "Experimental".

b) The letter A designates 1% aqueous AcOH (15 ml); B, 5% aqueous AcOH (25 ml); C, 38% (v/v) aqueous EtOH (70 ml); D, 33% (v/v) aqueous EtOH (90 ml).

c) Relative to the amount of the amine V.

d) Yields are of substances actually isolated and identified.

e) Unless otherwise stated, no attempt was made to recover V.

f) Actually, edetate disodium dihydrate was used.

IX ⟶ X).

Wenkert and Wickberg[9a] obtained the tetracycle X from V in 63% yield by oxidation with 10 molar equivalents of $Hg(OAc)_2$ in hot 5% aqueous AcOH for 1 h, followed by treatment with H_2S and $NaBH_4$ reduction of the over-oxidized product VI present as the minor component. Later on, several research groups applied this method to bicyclic piperidine derivatives, intermediates for the syntheses of tetracyclic and pentacyclic indole alkaloids,[9a,12] with or without modification. The main modification included the use of a combination of $Hg(OAc)_2$ and EDTA·2Na[12a-c] and of the solvent aqueous EtOH[12c] instead of aqueous AcOH. However, the yields of the cyclized products were only 20–45%.

In order to find an adequate oxidative cyclization procedure for high-yield conversion of V into X, we

thus investigated the effects of solvent, amount of $Hg(OAc)_2$–EDTA·2Na, temperature, and reaction time on the yield of X. It may be seen from Table 1 that in both the reactions in 1% aqueous AcOH and aqueous EtOH the presence of EDTA·2Na is necessary for high-yield formation of X. The use of 3 molar equivalents of $Hg(OAc)_2$–EDTA·2Na in boiling aqueous EtOH for 3 h (entry 11) is superior to any other variations listed in Table 1 since it produces the desired tetracycle X in acceptable yield at near neutrality with a minimized amount of the oxidizing reagent.

Thus, it is hoped that the present results would afford a sound basis for selection of reaction conditions when syntheses of more complex indoloquinolizidines possessing substituents in ring A and/or ring D will be designed through such an "oxidative cyclization route".

EXPERIMENTAL

General Notes —— All melting points are corrected. See ref. 1 or 4 for details of instrumentation and measurements. The following abbreviations are used: br = broad, d-d = doublet-of-doublets, m = multiplet, s = singlet. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University.

Indol-3-yl Piperidinomethyl Ketone (II) —— A solution of piperidine (I) (3.41 g, 40 mmol) and 3-chloroacetylindole[13] (3.87 g, 20 mmol) in $HCONMe_2$ (35 ml) was stirred at 80°C for 4.5 h. After cooling, the reaction mixture was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave a yellowish orange solid, which was recrystallized from 50% (v/v) aqueous EtOH to afford II (4.35 g, 90%) as pale yellow scales, mp 167–168°C (lit.[10] mp 169–170°C); ir ν_{max} (Nujol) 1635 cm^{-1} (ArCO); nmr ($CDCl_3$) δ: 1.3–1.8 (6H, m, CH_2's), 2.5–2.7 (4H, m, NCH_2's), 3.62 (2H, s, $ArCOCH_2$), 7.2–7.5 (3H, m, aromatic protons), 8.3–8.5 (2H, m, aromatic protons), 9.65 (1H, br, NH). Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.15; H, 7.58; N, 11.47.

α-(Piperidinomethyl)indole-3-methanol (III) —— A solution of II (7.51 g, 31 mmol) in EtOH (385 ml) was stirred under ice cooling, and $NaBH_4$ (5.86 g, 155 mmol) was added portionwise. After the solution was stirred at 20°C overnight, the solvent was removed by vacuum distillation. The residual solid was partitioned by extraction with a mixture of $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave III (7.48 g, 99%) as a yellow solid. Recrystallization from AcOEt produced an analytical sample as colorless scales, mp 147.5–148°C; nmr ($CDCl_3$) δ: 1.3–1.8 (6H, m, CH_2's), 2.2–2.9 (6H, m, NCH_2's), 4.17 (1H, br, OH), 5.09 [1H, d-d, J = 4.2 and 9.5 Hz, ArCH(OH)], 7.0–7.4 (4H, m, aromatic protons), 7.6–7.75 (1H, m, aromatic proton), 8.15 (1H, br, NH). Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.66; H, 8.35; N, 11.17.

Mercuric Acetate–EDTA·2Na Oxidation of V —— The following two procedures present typical examples of those employed for the runs listed in Table 1.

i) In Aqueous EtOH (Entry 11 in Table 1): A stirred mixture of V[9a] (457 mg, 2 mmol), EtOH (30 ml), and 0.1 M aqueous $Hg(OAc)_2$–EDTA·2Na·$2H_2O$ [1 : 1 (molar ratio)] (60 ml) was heated under reflux for 3 h. After cooling, the mixture was made alkaline (pH 9) with 3% aqueous NH_3 and stirred, after addition of $NaBH_4$ (757 mg, 20 mmol), at room temperature overnight. The reaction mixture was then made acidic (pH 3) with 10% aqueous HCl, and an insoluble substance was filtered off and washed with H_2O. The filtrate and washings were combined, made alkaline (pH 9–10) with 10% aqueous NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated in vacuo to leave a pale brownish solid (421 mg), mp 141–145°C. Purification of the solid by column chromatography [Al_2O_3 (10 g), $CHCl_3$ (50 ml)] yielded X (384 mg, 85%) as a slightly pinkish solid, mp 147–150°C, which was identical (by comparison of tlc behavior and ir spectrum) with an authentic sample.[8]

ii) In Aqueous AcOH (Entry 1 in Table 1): A stirred mixture of V[9a] (457 mg, 2 mmol), $Hg(OAc)_2$ (3.19 g, 10 mmol), EDTA·2Na·$2H_2O$ (3.72 g, 10 mmol), and 1% aqueous AcOH (15 ml) was kept at 110°C for 1.5 h. After cooling, the insoluble material that resulted was filtered off and washed with EtOH (16 ml). The filtrate and washings were combined, made alkaline (pH 9) with 10% aqueous NaOH, and stirred at room temperature overnight after addition of $NaBH_4$ (757 mg, 20 mmol). The reaction mixture was worked up in a manner similar to that described above under item (i), yielding X (363 mg, 80%) as a slightly brownish solid. Recrystallization from benzene–hexane (4 : 1, v/v) gave a pure sample, mp 151.5–152°C, which was identical with authentic X.[8]

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