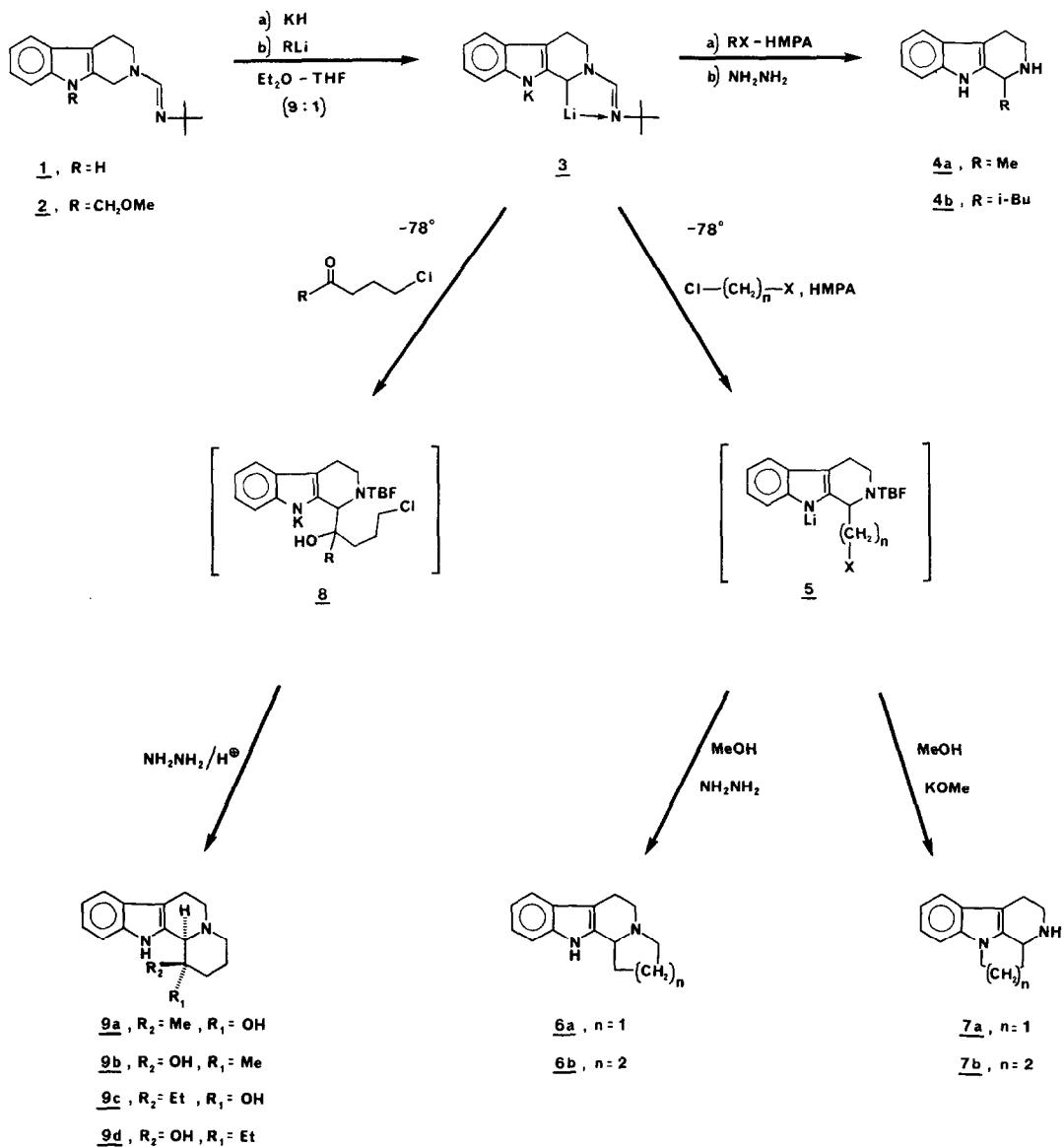


THE N-9, C-1 DIANION OF TETRAHYDRO- β -CARBOLINES.
REGIOSELECTIVE ALKYLATION LEADING TO INDOLE ALKALOID SYSTEMS

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Summary: By treatment of β -carboline formamidine (1) with potassium hydride followed by an alkyl lithium reagent, both the pyrrole proton (N-9) and the proton at C-1 are removed. The resulting dianion (3) alkylates cleanly at C-1 and ultimately at N-9 or N-2.

The presence of 1,2,3,4-tetrahydro- β -carbolines in numerous indole alkaloids has resulted in considerable activity with regard to their synthesis and elaboration¹. We recently described a novel route to elaborate β -carbolines using the formamidine 2, which exhibited useful chemical behavior for alkylation to tricyclic and tetracyclic derivatives². It was necessary to protect the pyrrole nitrogen prior to metalation of 2 due to the resistance of 1 to form a dianion with 2.0 equiv of organolithium bases. Because of this, several extra steps were necessary to reach the alkylated β -carbolines. This observation caused us to examine more closely the nature of the N-9, C-1 dianion. The removal of the pyrrole proton was readily accomplished with most bases (t -BuO⁻, NaH, KH, RLi), however the C-1 proton was totally inert when the pyrrole nitrogen was N-lithiated. We now can report that the C-1 proton is readily abstracted when the pyrrole is transformed to its sodio or potassio salt (5 equiv NaH or KH, ether: THF 9:1, 0°, 15 min). After cooling to -78°, addition of MeLi, n -BuLi, or t -BuLi affords the 1-Li derivative 3 by warming the solution to -25° for 15 min (t -BuLi), 45 min (n -BuLi), or 60 min (MeLi). Alkylation of 3 proceeded by addition of 1.5 equiv of HMPA to the red anion solution followed by cooling (-78° for RI; -45° for RBr) and stirring for 1 h. The reaction mixture was then treated with ethanol-water-acetic acid-hydrazine (v/v; 8:2:1:1) and allowed to stir at ambient temperature for 5 h. The reaction was diluted with water and ether extraction and acidic wash (NH₄Cl) gave an aqueous solution of 4 which was neutralized (10% KOH), extracted with ether, dried and



concentrated to give crude 4. Purification was accomplished by flash chromatography (silica gel, dichloromethane-methanol-Et₃N; 88:10:20) to give 4a (from methyl iodide) 86%, mp 177-178°² and 4b (from isobutyl bromide), 90%, mp (HCl) 261-262°². Thus the metalation-alkylation of 1 to 4 (a or b) was carried out in one vessel in very good yield.

It was now desirable to attempt the annelation sequences to 6, 7 and 9 using bifunctional electrophiles. When the dianion 3 was treated 1.5 equiv HMPA and then with 3-bromo-1-chloropropane (1.5 equiv, -45°) for 1 h, the red anion color disappeared and the hydrazine-acetic acid-aq. ethanol solution was added. After stirring at room temperature (15 h), the reaction was worked up, as described above, to furnish 6a in 68% yield, mp 173-174°³. Similarly, addition of 4-bromo-1-chlorobutane gave 6b in 77% yield, mp 151-152°². In order to effect cyclization of 5 toward the pyrrole nitrogen (to 6) it was found that the pyrrole-K anion underwent metathesis to the N-Li anion (5) on alkylation with the dihaloalkanes. Thus the LiBr generated, in going to 5, resulted in metal exchange (due to precipitation of KBr in the THF solution). Because of this, no alkylation to 6 could be observed. However, addition of 3 equiv methanol to 5, with the excess KH present (*vide supra*), transformed the N-Li of 5 into the N-K salt due to the equilibrium favoring LiOMe⁴. The cyclization of 5 (N-K salt) proceeded by simply stirring the solution, after MeOH addition, at room temperature for 24-36 h. Formamidine cleavage to 7a or 7b was performed by addition of the hydrazine-acetic acid solution and stirring overnight (25°). Workup, as above, gave 7a (53%, mp (HCl) 244-245°) and 7b (71%, mp 134-135°).

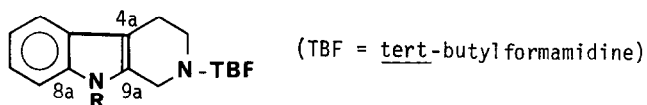
Finally, 3 was treated with 5-chloro-2-pentanone and 6-chloro-3-hexanone (THF -78°, 40 min, no HMPA required in reaction of 3 with carbonyls) and gave 8 which was treated directly with the hydrazine-acetic acid (2 h, 25°) and worked up as above. The crude materials 9 (a, b) and 9 (c, d) were flash chromatographed (EtOAc-MeOH-Et₃N; 300:10:5) to give pure 9a (55%, mp 202-203°³) and 9b (7%, mp 208-210°⁵) and, for the homologous ketone, pure 9c (19.5%, mp 179-180°⁵) and 9d (60%, mp 187-189°⁶). Thus, the stereoselectivity of 9a-9b was 8.5:1 whereas the selectivity for 9c-9d was somewhat less (3:1). Nevertheless, the major products 9a and 9d could be isolated pure in 55% and 60% yields, respectively.

This facile approach to indole alkaloids systems possesses considerable merit and further studies, including asymmetric alkylation of 3, is in progress.

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REFERENCES AND NOTES

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2. Meyers, A. I., Hellring, S. J. Org. Chem. 1982 47, 2229.
3. Satisfactory elemental, mass and spectral analyses were obtained.
4. Lithium-potassium exchange, or lack thereof, was confirmed by ^{13}C -NMR using DMSO-d_6 solutions (0.38 M) and observing the chemical shifts of the indicated carbons.



<u>R</u>	<u>Salt Added</u>	<u>δ_{8a}</u>	<u>δ_{9a}</u>	<u>δ_{4a}</u>	<u>Comments</u>
H	--	135.8	131.5	106.7	
Li	--	141.5	137.5	103.5	
Li	(3.0 eq) KI	141.5	137.6	103.4	No exchange of Li
Li	(3.0 eq) <i>t</i> -BuOK	146.9	143.3	100.6	Complete exchange to K
K	--	146.9	143.3	100.4	
K	(3.0 eq) LiOMe	146.9	143.3	100.3	No exchange of K
K	(3.0 eq) LiI	142.8	138.9	102.9	Exchange to Li

The above data clearly show that LiOR is a tighter ion pair than LiNR₂ and 5 is readily transformed into the potassio-salt on addition of MeOK.

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6. Hammer, H., Winterfeldt, E. Tetrahedron 1981 37, 3609; reports mp 186°.

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