A Total Synthesis of Alstonilinol

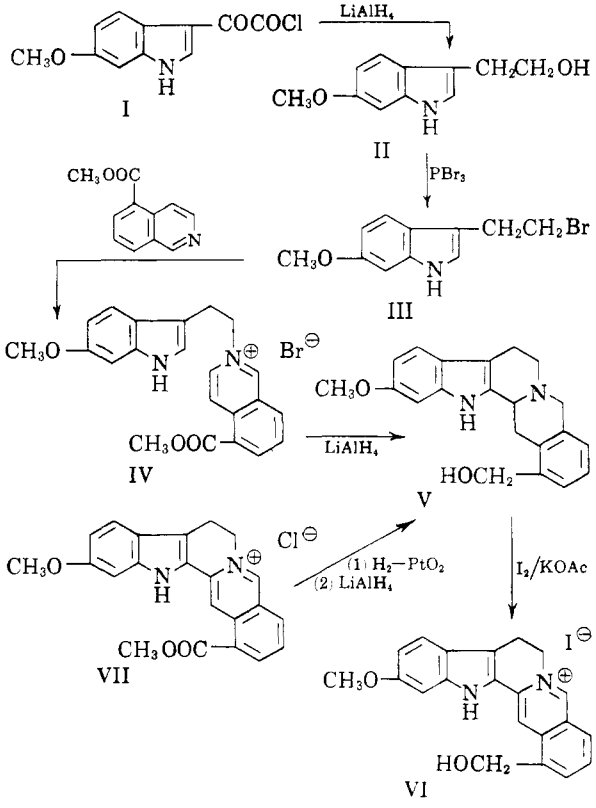
Sir:

In 1942 a minor alkaloidal constituent, alstoniline, was isolated from the tree bark of *Alstonia constricta F. Muell.*[1] On the basis of its degradation to 2-methylisophthalic acid and norharmine taken together with spectrographic data for a synthetic analog in which Ring C was open, a structure (VII) was proposed for alstoniline.[2,3]

We now wish to announce a total synthesis of alstonilinol which confirms the structure previously assigned to alstoniline. This is a direct result of investigations of the action of metal hydrides on β-(3-indolyl)ethyl-1-pyridinium and -2-isoquinolinium salts.[4]

6-Methoxyindole with oxalyl chloride yields 6-methoxy-3-indolylglyoxalyl chloride (I) in 86% yield.[5] On reduction with lithium aluminum hydride in tetrahydrofuran I gave 6-methoxytryptophol (II), white plates, m.p. 96–97°, in 79% yield (*Anal.* Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.91; N, 7.16). Condensation of the unstable β-(6-methoxy-3-indolyl)ethyl bromide (III) with 5-carbomethoxyisoquinoline[6] gave β-(6-methoxy-3-indolyl)ethyl-5-carbomethoxyisoquinolinium bromide (IV) as orange clumps, m.p. 270° (dec.), in 68% yield from 6-methoxytryptophol (*Anal.* Calcd. for $C_{22}H_{21}BrN_2O_3$: C, 59.85; H, 4.77; N, 6.35. Found: C, 59.97; H, 4.78; N, 6.35). Reductive ring closure of IV with lithium aluminum hydride in ether[7] gave tetrahydroalstonilinol (V), fine white needles from chloroform–petroleum ether, m.p. 220–224°, in 64% yield (*Anal.* Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.28; H, 6.77; N, 8.09). The hydrochloride formed white needles, m.p. 278° (dec.), from absolute alcohol (*Anal.* Calcd. for $C_{21}H_{22}N_2O_2 \cdot HCl$: C, 68.03; H, 6.29; N, 7.51. Found: C, 67.97; H, 6.01; N, 7.29). Tetrahydroalstonilinol and its hydrochloride as thus prepared furnished infrared spectra identical in all respects with the compounds prepared from alstoniline.[2]

Dehydrogenation of V with iodine and potassium acetate in methanol gave alstonilinol iodide (VI) as orange clumps of needles, m.p. 320° (dec.), from methanol in 90% yield (*Anal.* Calcd. for $C_{21}H_{19}INO_2$: C, 54.90; H, 4.17; N, 6.10; I, 27.86. Found: C, 55.02; H, 4.20; N, 6.07; I, 27.52).



The structure previously assigned to alstoniline is thus confirmed. Further, it appears that reductive ring closure of β-(3-indolyl)ethyl-2-isoquinolinium bromides is capable of wide application in the synthesis of pentacyclic β-carbolines. Ring closure apparently occurs exclusively between the 2 position of the indole and the 3 position of the isoquinoline ring systems.

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