Synthesis of 1,2,3,4,11,11a-Hexahydro-6*H*-pyrimido[2,3-*b*]isoquinoline, a Novel Heterocyclic Ring System

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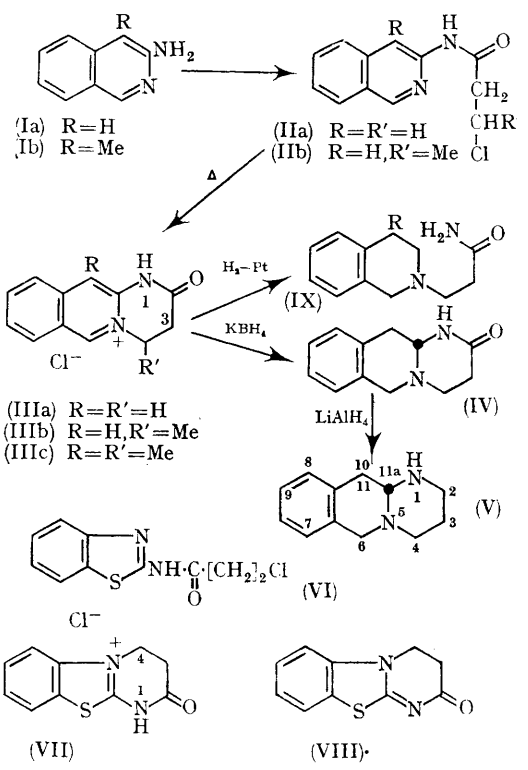
DURING our studies with 3-aminoisoquinoline and related compounds as potential antimalarial drugs,[1] we have synthesized 3,4,11,11a-tetrahydropyrimido[2,3-*b*]isoquinolin-2(1*H*)one (IV) and 1,2,3,4,11,11a-hexahydro-6*H*-pyrimido[2,3-*b*]isoquinoline (V), incorporating a new 1,3-diazatricyclic ring system by a readily accessible route. The synthesis of the ω-chloroalkyl amides (II) generally proceeded without difficulty when the appropriate chloroacyl chloride was allowed to react with the aminoisoquinoline[2] (I) in dry benzene. These ω-chloroalkyl amides could then readily react with secondary amines. However, we observed on fusion of 3-chloro-*N*-(isoquinolin-3-yl)propionamide (IIa), m.p. 157—158°, that the compound resolidified in the melting point tube at *ca.* 165°. When (IIa) was fused at *ca.* 165° on a preparative scale, a yellow solid which could be recrystallized from methanol was obtained in 70% yield. This compound was assigned structure (IIIa) (2-oxo-1,2,3,4-tetrahydropyrimido[2,3-*b*]isoquinolin-5-ium chloride), m.p. 318° (decomp.),† on the basis of its elemental analysis‡ and spectroscopic data [ν (KBr): 1750, 1655, and 1650 cm.$^{-1}$; λ_{max} (MeOH): 218 mμ (ε 17,900), 245 (ε 41,000), 251 (ε 40,000), and 315 (ε 8350)]. Similarly, the 3-chlorobutyramide (IIb) was cyclized to the corresponding 4-methyl derivative (IIIb), m.p. 274—275·5° [λ_{max} (MeOH): 219 mμ (ε 16,000), 247 (ε 36,200), 252 (ε 37,000), 288 (ε 5850), 300 (ε 6220), and 315 (ε 7700)]. The synthesis of 1,2,3,4-tetrahydro-4,11-dimethyl-2-oxopyrimido[2,3-*b*]isoquinolin-5-ium chloride (IIIc) (m.p. 313°, decomp. 315°)[3] was carried out by an analogous sequence of reactions from 3-amino-4-methylisoquinoline (Ib), m.p. 116·5—118° (lit.,[3] m.p. 122—124°). The generality of this cyclization could be demonstrated: when 2-(3-chloropropionylamino)benzothiazole (VI), m.p. 186—187°, was fused at 190°, a product was obtained to which we assign the structure (VII), 1,2,3,4-tetrahydro-2-oxopyrimido[2,1-*b*]benzothiazol-5-ium chloride, m.p. 279° (decomp.); λ_{max} (EtOH): 251 mμ (ν 9200), 301 (ε 19,800). The synthesis of (VIII) by the reaction of equimolar quantities of 2-aminobenzothiazole and β-chloropropionyl chloride in alkaline medium has recently been reported[4].

The reduction of the quaternary salt (IIIa) to produce the novel heterocyclic ring system, 3,4,11,11a-tetrahydropyrimido[2,3-*b*]isoquinolin-2-(1*H*)-one (IV), was attempted in several ways before satisfactory conditions were found. Our initial attempts at catalytic reduction of (IIIa) with platinum oxide in methanol resulted only in the isolation of a low-melting solid, m.p. 78—81°,



which, on the basis of spectral data and independent synthesis from tetrahydroisoquinoline and 3-chloropropionamide, was identified as the ring-cleavage product, 1,2,3,4-tetrahydroisoquinoline-2-propionamide (IX). Lithium aluminium hydride reduction of (IIIa) in several solvent systems failed to yield any identifiable products. However, the reduction of (IIIa) with potassium borohydride in ethanol–water resulted in the isolation of the tricyclic lactam (IV) in 30—40% yield as a crystalline product, m.p. 190—192° [ν (KBr): 1365 and 1670 cm.$^{-1}$; λ_{max} (MeOH): 257

(ε 290), 264 (ε 400), and 271 mμ (ε 4422)]. The n.m.r. spectrum of (IV) obtained in $CDCl_3$ solution at 60 Mc./sec. shows δ 2·62 (m, $CO{\cdot}CH_2{\cdot}CH_2$) 3·0 (m, $N{-}CH_2CH_2$); 3.54, [d, *J* 15 $PhC(H_{ax})$-H–N]; 3·96 (dd, *J* 9, 5 $CH_2CH{-}[N]_2$); 4·04 [d, *J* 15 $PhC(H_{eq})H{-}N$]; 7·12 (s, 4 aromatic H); 8·35 (s, N–H).

Thermodynamic and conformational considerations require the ring juncture to be 5, 11a-*trans*. This assignment is supported by the n.m.r. coupling constants for the 5-proton (δ 3·96 dd, *J* 9, 5) and the presence of "Bohlmann bands" in the i.r. spectrum.[5]

A small amount of the ring-opened product (IX) was also isolated (and identified as its perchlorate salt) from the borohydride reduction mixture. The further reduction of (IV) to 1,2,3,4,11,11a-hexahydro-6*H*-pyrimido[2,3-*b*]isoquinoline (V) was carried out in 80% yield with lithium aluminium hydride in ether. An oily product was obtained which solidified, m.p. 68—69·5°, when thoroughly dried *in vacuo*. Sublimation of this compound at 0·3 mm. yielded white crystals, m.p. 70—72°. The i.r. spectrum of (V) lacks absorption in the carbonyl region and indicates the "*trans*" ring juncture by the presence of "Bohlmann bands".[5] The n.m.r. spectrum is compatible with these assignments.

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† Determined on a Dupont 900 Differential Thermal Analyzer under nitrogen.
‡ Satisfactory elemental analyses were obtained for all compounds reported.

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