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SOME REACTIONS OF 1H-PYRROLO[3,4-b]QUINOLINE DERIVATIVES

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In connection with an approach for synthesizing antitumor and antileukemic alkaloid, camptothecin (I), we wish to report our findings on some reactions of 1H-pyrrolo[3,4-b]quinoline derivatives.

Condensation of aniline with 1,4-diethoxycarbonyl-3-oxopyrrolidine (2) using calcium sulfate as a dehydrating reagent in the presence of catalytic amount of acetic acid gave an excellent yield of the anile (I), which was converted into 2-ethoxycarbonyl-9-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-b]quinoline (II) by thermal cyclization in refluxing diphenyl ether (1g)*1. The compound (II) was treated with phosphorus oxychloride in chloroform to give the 9-chloro derivative (III), mp 203°. This was led to 9-methoxy-2,3-dihydro-1H-pyrrolo[3,4-b]quinoline (V), the dihydrochloride mp 270°, via IV by treating with sodium methoxide subsequent alkaline hydrolysis. Several homologous compounds of V containing chloro, methoxy, or methyl substituent on its benzene ring were also prepared by use of the same procedure. Catalytic reduction of III using palladium-carbon in ethanol -dioxane followed by hydrolysis gave 2,3-dihydro-1H-pyrrolo[3,4-b]quinoline (VI), the dihydrochloride mp 250-252°.

On the other hand, attempts to obtain VI by complex metal hydrides reduction of 1-oxo-2,3-dihydro-1H-pyrrolo[3,4-b]quinoline (VIII) or its 2-benzyl derivative (IX), both of which were derived from methyl 2-methylquinoline-3-carboxylate via the bromide (VII) by bromination with N-bromosuccinimide followed by lactamation with ammonia or benzyl amine, failed (1g). Sodium bis-(2-methoxyethoxy) aluminum

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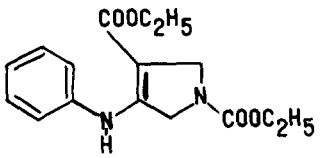
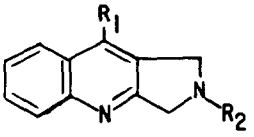
*1 When the present studies have been completed, Shamma and Novak reported the same findings independently.



(I)



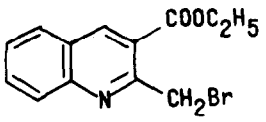
(II) R_1= OH R_2= $COOC_2H_5$

(III) R_1= Cl R_2= $COOC_2H_5$

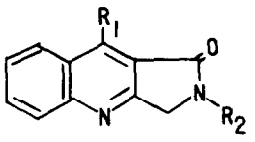
(IV) R_1= OCH_3 R_2= $COOCH_3$

(V) R_1= OCH_3 R_2= H

(VI) R_1= H R_2= H



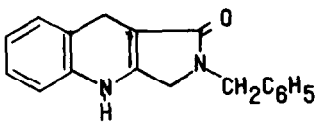
(VII)



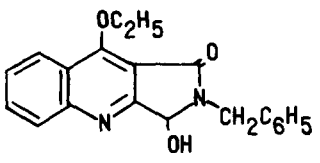
(VIII) R_1= H R_2= H

(IX) R_1= H R_2= $CH_2C_6H_5$

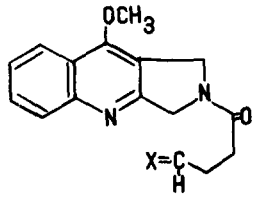
(X) R_1= OC_2H_5 R_2= $CH_2C_6H_5$



(XI)

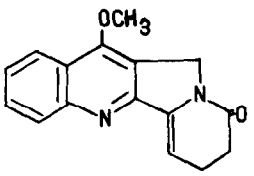


(XII)

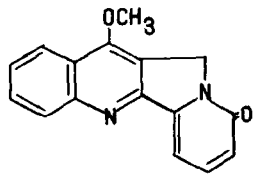


(XIII) X= $(-OC_2H_5)_2$

(XIV) X= O



(XV)



(XVI)

hydride (SDMA) reduction (3) of IX afforded 2-benzyl-1-oxo-2,3,4,9-tetrahydro-1H-pyrrolo[3,4-b]quinoline (XI) [mp 187-190° (dec.); IR ν(nujol): 3170, 1675cm^{-1}; NMR (d_6-DMSO) τ: 6.12 (2H, s.), 5.93 (2H,s.), 5.25 (2H, s.), 2.10-3.16 (9H, m.); MS m/e: 276 (M^+)] in 52% yield. The same reduction product (XI) was also isolated in the case of using lithium aluminum hydride. This compound was susceptible to oxidation and reverted to the starting material during recrystallization.

Reduction of the 9-ethoxy derivative (X) with SDMA gave rise to 2-benzyl-9-ethoxy-3-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-b]quinoline (XII) [mp 228-229°; IR ν (nujol): 3400, 1695, 1610cm^{-1}; UV λ_{max}^{MeOH}mμ(ε): 290 (10100), 240 (47200); NMR ($CDCl_3$) τ: 8.48 (3H, t., J=8Hz.), 5.26 and 5.46 (2H, q., J=14Hz. AB type, -$\dot{N}$-C$\underline{H_2}$-) 4.04 (1H, s., -O-C$\underset{\sim}{H}$-$\dot{N}$-), 1.52-2.80 (9H, m.)] as a minor product, though not the real reduction product. The major part was intractable neginous material which we presumed to be 9-ethoxy-2-benzyl-2H-pyrrolo[3,4-b]quinoline from the consideration of its mass spectrum [m/e 302 (M^+), (M^+ of X minus 16)] (4).

Condensation of the free base (V) with β-formyl propionic acid diethyl acetal using dicyclohyxyl carbodiimide in chloroform at room temperature afforded the amide-acetal (XIII) [mp 119-121°; IR ν(nujol): 1645cm^{-1}; MS m/e: 358 (M^+)], which gave the corresponding amido-aldehyde (XIV) [IR ν(nujol): 2710, 1710, 1633 cm^{-1}] on being treated with dilute hydrochloric acid. Intramolecular cyclization of XIV with refluxing acetic anhydride gave a tetracyclic lactam (XV) [mp 178-180 °; IR ν(nujol): 1659, 1608cm^{-1}; UV λ_{max}^{EtOH}mμ(ε): 352 (6850), 297 (11250), 245 (53000); NMR ($CDCl_3$) τ: 7.30-7.50 (4H, doublet type), 5.85 (3H, s.), 4.88 (2H, s.), 3.83-4.00 (1H, m.); MS m/e: 266 (M^+)] in 42% yield. The compound (XV) was then dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene to yield 7-methoxy-4-oxo-4H-indolizino[1,2-b]quinoline (XVI) [mp 238-239° (dec.); IR ν(nujol): 1646, 1590cm^{-1}; UV λ_{max}^{EtOH}mμ(ε): 350 (19120), 255 (31640), 247 (27530), 219 (44560); NMR ($CDCl_3$-TFA) τ: 5.26 (3H, s.), 4.05 (2H, s.), 1.33-2.93 (7H, m.); MS m/e: 264 (M^+)] as yellow rhombs.

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