ON CARDIOACTIVE STEROIDS V.[1] SYNTHESIS OF THE PYRIDONE ANALOGUE OF BUFALIN

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Abstract -- An efficient and simple synthesis of azabufalin (2) from compound (4) derived from testosterone is reported.

The recent communication of Wicha and Masnyk[2] on the synthesis of the pyridone derivative (1) prompts us to report the preparation of azabufalin (2) which we have completed about a year ago.[3] The fact that the Polish authors chose to report their work serves to underline the difficulty inherent in setting up simultaneously both the β-configuration at C_{17} and the substitution and natural configuration at C_{14}. It will be clear from the sequel that our general synthetic strategy[4] which we have developed for the synthesis of cardenolides can overcome this difficulty very simply.

The lithium derivative (3) was prepared by treatment of 5-bromo-2-methoxypyridine[5] with n-butyllithium in ether at -70°C. Addition of the ketone (4)[4] to this solution of (3) yielded compound (5), mp 109-111°C (85% after recrystallization from hexane-ether);† pmr ($CDCl_3$): δ = 0.88 (s, 3H, 19-CH_3), 1.07 (s, 3H, 18-CH_3), 3.93 (s, 3H, OCH_3).

Acetylation of (5) with acetic anhydride and pyridine in the presence of 4-dimethylaminopyridine yielded the acetyl derivative (6), mp 161-163°C (crystallized from methanol, yield 91%); ir ($CHCl_3$): 1735 CM^{-1} (C=O).

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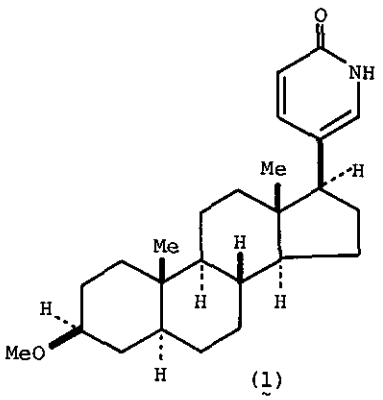
†All compounds gave correct molecular ions in mass spectrometry and spectral data consistent with the structures assigned to them. All crystalline compounds gave acceptable C, H, O, N elemental analyses.



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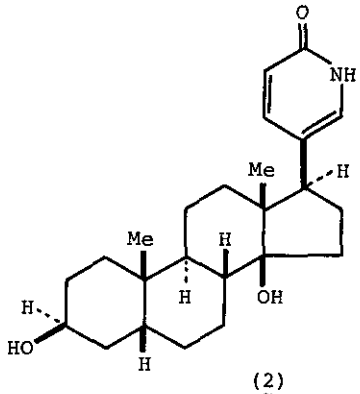

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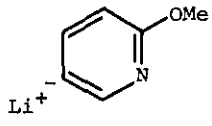

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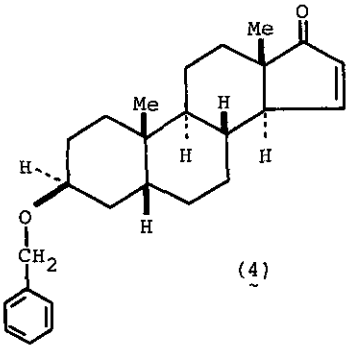

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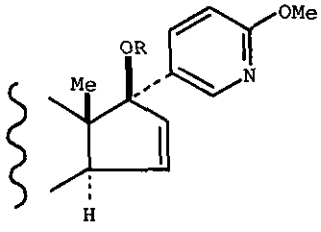
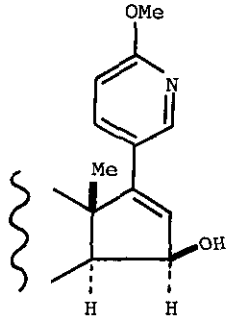


(5) [R = H]

(6) [R = -C(=O)CH3]



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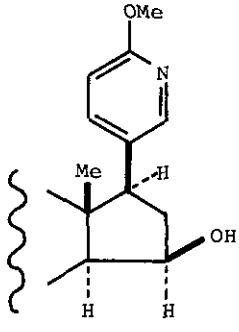

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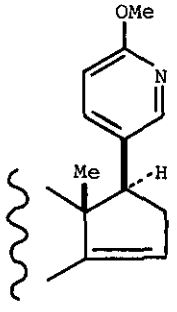

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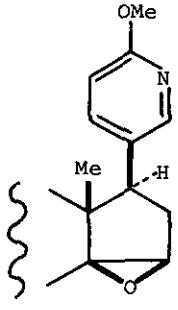

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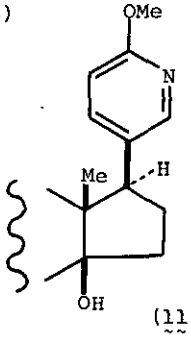

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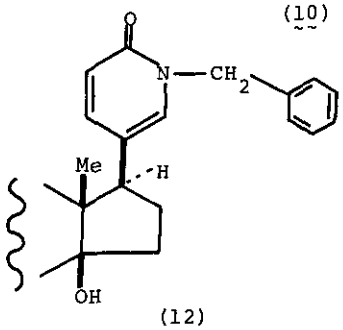

(12)

The allylic rearrangement of compound (6) was accomplished by reflux in aqueous acetone in the presence of $CaCO_3$ for 48 h. The product (7) (mp 94-95°C) [pmr ($CDCl_3$): δ = 3.93 (s, 3H, OCH_3), 4.54 (broad s, 1H, $C_{15}H$), 5.95 (d, 1H, J = 3 Hz, $C_{16}H$)] was obtained in a yield of 84% after crystallization from ether-hexane.

The allylic alcohol (7) was hydrogenated in ethanol over 10% $Pd/CaCO_3$. The dihydro derivative (8) was obtained as a foam in a yield of 96%. Elimination of the C_{15} hydroxyl in compound (8) was accomplished by treatment with methanesulfonyl chloride in pyridine. The reaction was fully regiospecific and gave the olefin (9) (mp 94-95°C) in a yield of 85% after crystallization from acetone [pmr ($CDCl_3$): δ = 3.93 (s, 3H, OCH_3), 5.3 (broad s, 1H, $C_{15}H$)].

The olefin (9) was treated with N-bromosuccinimide in aqueous acetone at room temperature for 30 min and the crude bromohydrin was stirred with alumina in a mixture of acetone and CH_2Cl_2. The β-epoxide (10) (mp 140-141°C)[††] [pmr ($CDCl_3$): δ = 0.62 (s, 3H, 18-CH_3), 0.98 (s, 3H, 19-CH_3), 3.51 (broad s, 1H, $C_{15}H$), 3.90 (s, 3H, OCH_3)] was obtained in a yield of 74% after crystallization from hexane-ether.

Reduction of the epoxide (10) with $LiAlH_4$ in tetrahydrofuran under reflux gave the 14β-alcohol (11) (mp 103°C) [ir ($CHCl_3$): 3616 cm^{-1} (-OH); pmr ($CDCl_3$): δ = 0.57 (s, 3H, 18-CH_3), 0.94 (s, 3H, 19-CH_3), 3.91 (s, 3H, OCH_3)] in a yield of 74% after crystallization from ether-hexane.

Compound (11) was refluxed for 24 h with potassium carbonate and benzyl bromide in acetone. The N-benzylpyridone derivative (12) (mp 256-257°C) [uv λ_{max}^{MeOH}: 233 nm (ε = 10,340), 312 nm (ε = 5,311); ir ($CHCl_3$): 3612 (OH), 1665 cm^{-1} (CON); pmr ($CDCl_3$): δ = 4.47 (s, 2H, -O-CH_2-Ph), 5.08 (s, 2H, N-CH_2-Ph)] was obtained in a yield of 52% besides 40% recovered starting material and recrystallized from CH_2Cl_2-ether.

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[††]The α-epoxide of compound (9) (mp 164°C) was obtained by the action of m-chloroperbenzoic acid and it was converted to the β-epoxide (10) via the 14β, 15α-diol (mp 96°C).

Finally, hydrogenation of compound (12) over palladium on charcoal in a mixture of dioxane and ethanol removed both benzyl groups and yielded the desired azabufalin (2) (mp 299-301°C) [uv λ_{max}^{MeOH}: 231 nm (ε = 12,360), 307 nm (ε = 6,161); ir (KBr): 1658 cm^{-1} (CON); pmr ($CDCl_3$-DMSO-d_6): δ = 0.60 (s, 3H, 18-CH_3), 0.92 (s, 3H, 19-CH_3), 6.30 (d, 1H, J = 9 Hz, $C_{23}H$), 7.12 (broad s, 1H, $C_{21}H$), 7.75 (poorly resolved dd, 1H, $C_{22}H$)][†††] which was recrystallized from methanol-ether.

ACKNOWLEDGEMENTS

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[†††] In a number of more soluble derivatives of this series a doublet of doublets (J = 9 Hz and 3 Hz) in good agreement with reference (2) was found for the C_{22} hydrogen.

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