

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.

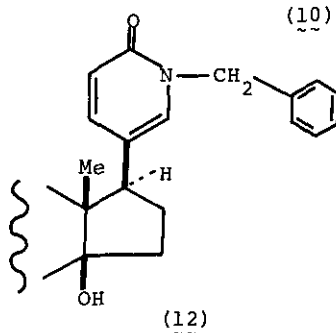
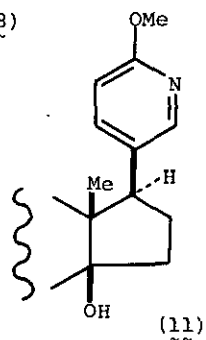
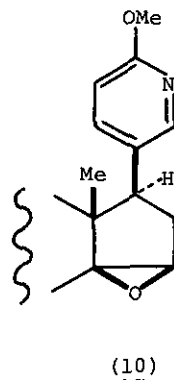
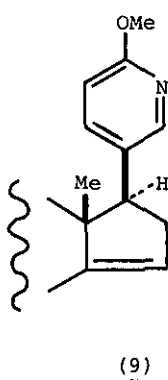
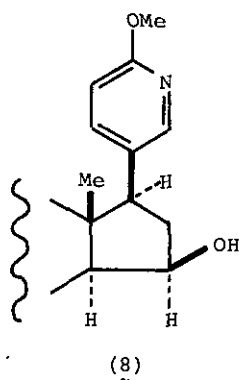
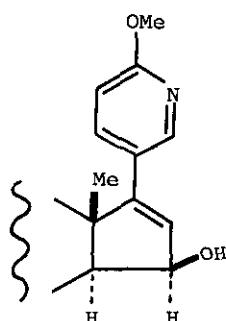
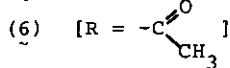
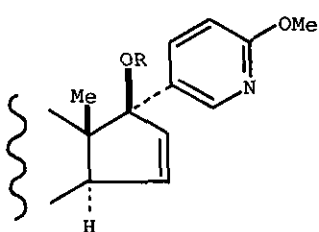
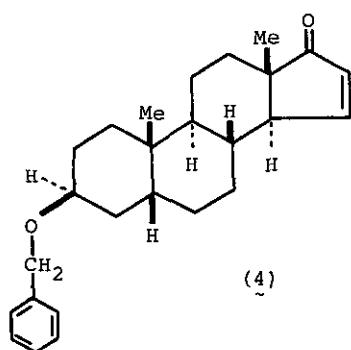
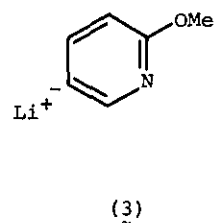
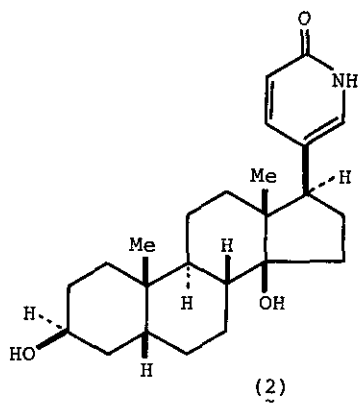
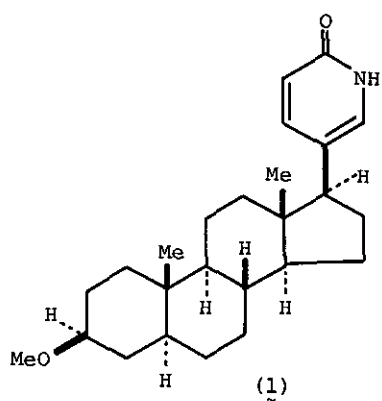
The recent communication of Wicha and Masnyk² on the synthesis of the pyridone derivative (1) prompts us to report the preparation of azabufalin (2) which we have completed about a year ago.³ The fact that the Polish authors chose to report their work serves to underline the difficulty inherent in setting up simultaneously both the β -configuration at C₁₇ and the substitution and natural configuration at C₁₄. It will be clear from the sequel that our general synthetic strategy⁴ 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-methoxy-pyridine⁵ 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 (CDCl₃): δ = 0.88 (s, 3H, 19-CH₃), 1.07 (s, 3H, 18-CH₃), 3.93 (s, 3H, OCH₃).

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 (CHCl₃): 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.



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 methane-sulfonyl 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 14 β -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 $\lambda_{\text{max}}^{\text{MeOH}}$: 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 14 β , 15 α -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 $\lambda_{\text{max}}^{\text{MeOH}}$: 231 nm ($\epsilon = 12,360$), 307 nm ($\epsilon = 6,161$); ir (KBr): 1658 cm^{-1} (CON); pmr (CDCl_3 -DMSO- d_6): $\delta = 0.60$ (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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