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STUDIES DIRECTED TOWARD SYNTHESIS OF QUASSINOIDS - I. CONVERSION OF CHOLIC ACID TO A δ-LACTONE

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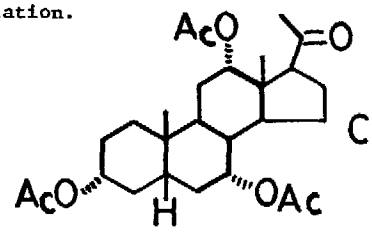
The broad spectrum of biological properties[1], including antileukemic activity[2], associated with quassinoid related principles from the plant family *Simaroubaceae* has attracted considerable interest.[3] Prompted by the suggestion that the conjugated ketone in the A-ring of quassinoids may play an active role in their mechanism of biological action[4], one research group has simulated the diosphenol system of quassinoids by incorporating it in the A-ring of an androstane skeleton.[5] Another group has recently communicated their preliminary results toward the synthesis of quassin starting with a Diels-Alder reaction as the intial step.[6] The purpose of this communication is to report the preparation of a D-seco steroid and its conversion to a δ-lactone with a quassin stereochemistry at C-7.

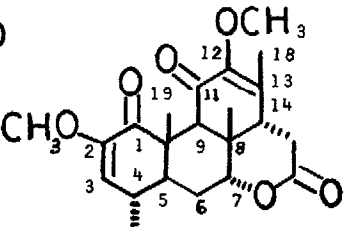
Employing the Barbier-Wieland side-chain degradation sequence, methyl cholate was converted to ketone *1*.[7] Reaction of one equivalent of Br_2 with *1* in presence of HBr gave the corresponding 17-bromoketone which underwent efficient dehydrobromination by heating in HMPA[8] under an atmosphere of dry N_2 giving enone *2*[ϑ_{max} 1670 cm^{-1}, λ_{max} =236nm, pmr 6.67δ (t, 1p, C-16)]. Ozonolysis of enone *2* in dry EtOAc at -78° followed by treatment of the resulting ozonide with HOAc containing 30% H_2O_2 afforded diacid *3* in up to 70% yield. Reaction of *3* with diazomethane provided diester *4* [pmr ($CDCl_3$, int tms) 5.13 (peak, 1p, 12β-H), 4.87 (peak, 1p, 7β-H), 4.53 (hump, 1p, 3β-H), 3.62 (s, 6p, OCH_3), 2.10 & 2.07 & 2.03 (3s, 3p ea, 3α-OAc & 7α-OAc & 12α-OAc), 1.17 (s, 3p, C-18), and 0.93 (s, 3p, C-19)δ; mass spec m/e 524(M^+)]. Diester *4* was successively treated with 2% KOH in CH_3OH, acid, diazomethane, and acetic anhydride-pyridine to yield δ-lactone *5* [mp 233-5°; pmr (CDCl , int tms) 5.10 (peak, 1p, 12β-H), 4.63 (hump, 1p, 3β-H), 4.20 (hump, 1p, 7β-H), 3.58 (s, 3p, OCH_3), 1.98 (s, 6p, 3α-OAc & 12α-OAc), 1.22 (s, 3p, C-18), and 0.78 (s, 3p, C-19)δ; mass spec m/e 450(M^+)].

Inspection of Drieding models suggests that the most likely stereochemistry for δ-lactone *5* would have rings A and C in chair conformations and ring-B and the lactone ring in boat conformations; i.e., the B-ring chair conformation in diester *4* becomes a boat conformation in lactone *5*. The substantial change in the pmr chemical shifts of the 7β-H (also broadens from a peak to hump showing that it goes from an equatorial position

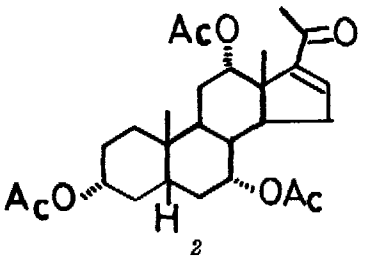
to an axial-like position) and C-19 methyl in going from ester *4* to lactone *5* as compared to the 3β-H and 12β-H and C-18 methyl chemical shifts is in agreement with this interpretation.



1



Quassin



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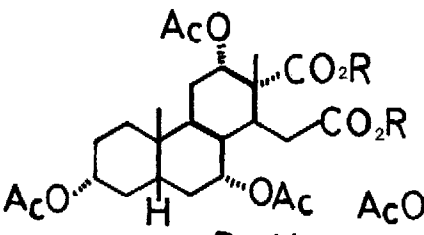
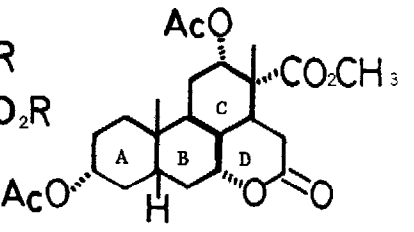


3 R=H

4 R=CH$_3$



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References and Footnotes

1. A. Gaudemer and J. Polonsky, *Phytochem.*, *4*, 149 (1965); K. Y. Sim, J. J. Sims, and T. A. Geissman, *J. Org. Chem.*, *33*, 429 (1968); W. Stocklin, L. B. DeSilva, and T. A. Geissman, *Phytochem.*, *8*, 1565 (1969).
2. S. M. Kupchan, R. W. Britton, J. A. Lacadie, M. F. Ziegler, and C. W. Siegel, *J. Org. Chem.*, *40*, 648 (1975).
3. For examples, see T. Murae, T. Tsuyuki, T. Ikeda, T. Nishihama, S. Masuda and T. Takahashi, *Tetrahedron*, *27*, 5147 (1971) and J. Polonsky, Z. Baskevitch, H. E. Gottlieb, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, *40*, 2499 (1975).
4. S. M. Kupchan and J. A. Lacadie, *J. Org. Chem.*, *40*, 654 (1975).
5. H. J. Koch, H. Pfenninger, and W. Graf, *Helv. Chim. Acta*, *58*, 1727 (1975).
6. N. Stojanac, A. Sood, Z. Stojanac, and Z. Valenta, *Can. J. Chem.*, *53*, 619 (1975).
7. All compounds exhibited satisfactory spectral and C,H microanalytical data.
8. R. Hanna, *Tetrahedron lett.*, 2105 (1968).