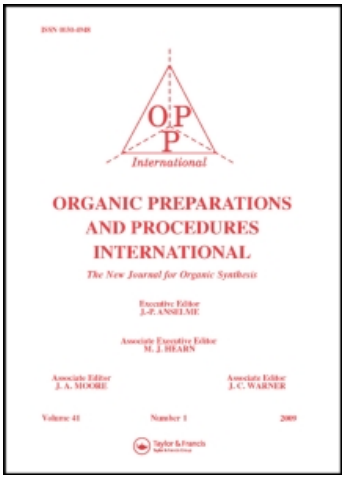

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AN IMPROVED SYNTHESIS OF 5β-CHOLEST-3-ENE

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(By J.-P. Anselme, Editor)

AN IMPROVED SYNTHESIS OF 5β-CHOLEST-3-ENE

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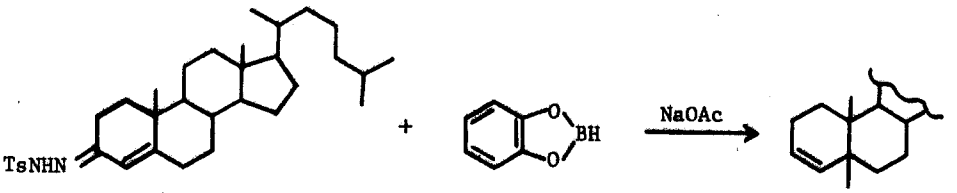
The selective reduction of tosylhydrazones of α,β-unsaturated carbonyl compounds to alkenes with catecholborane (I) occurs with migration of the double bond and is a high-yield, regiospecific and stereospecific reaction.[1] The tosylhydrazone of 4-cholesten-3-one (II) is quantitatively reduced to a mixture of 92% 5β-cholest-3-ene (III) and 8% of 5α-cholest-3-ene from which III is isolated in 89% yield.



II I H III

The literature reveals the 5β-cholest-3-ene is difficult to obtain. For example, the Wolff-Kishner reduction of II yields only the more thermodynamically stable 5α isomer (overall yield <2%),[2] which dehydrohalogenation of 3β-chloro-5β-cholestane gives a mixture of 5α- and 5β-cholest-3-ene in a 55:45 ratio but no overall yield was stated.[3] III has been prepared in an unspecified yield, by heating the epimeric 4β-bromo-3-hydroxy-5β-cholestanes to reflux in acetic acid.[3]

EXPERIMENTAL

The tosylhydrazone of 4-cholesten-3-one[4] (4.98 g, 9 mmoles) is introduced into a dry, nitrogen flushed, 100 ml one-necked flask equipped with a magnetic stirring bar, a side arm fitted with a rubber stopple and a reflux condenser connected to a mercury bubbler. Twenty ml of chloroform is introduced to dissolve the tosylhydrazone and the solution is cooled to 0° while maintaining a nitrogen atomsphere. Catecholborane (1.21 ml, 10.8 mmoles, 20% excess)[5] is introduced *via* a hypodermic syringe and the solution is stirred for two hours at 0°. Sodium acetate trihydrate (2.5 g, 18 mmoles) and 20 ml of chloroform are added and the mixture is allowed to warm to room temperature (about 30 min.) The mixture is then gently heated to reflux (oil bath) for 1 hr. The mixture is cooled and filtered and the residue is washed with 50 ml of chloroform. The combined filtrates are concentrated on a rotary evaporator and the concentrate is chromatographed on 200 g of neutral alumina (activity 1) with hexane.[6] The product is collected in 200 ml fractions; all of the product, 2.95 g (89%), was found in the second fraction as a colorless oil.[7]

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† Department of Chemistry, University of Arkansas at Little Rock, Little Rock, Arkansas 72204

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2. G. M. L. Cragg, C. W. Davey, D. N. Hall, E. E. Richards and T. L. Whateley, J. Chem. Soc., (C), 1266 (1966).

3. G. Bellucci, F. Macchia and V. Maloguzzi, Tetrahedron Lett., 4973 (1966).

4. 4-Cholesten-3-one tosylhydrazone, mp. 131-132°, was prepared according to the procedure of R. O. Hutchins, C. A. Milervsky and B. Maryanoff, J. Am. Chem. Soc., 95, 3662 (1973).

5. Available from Aldrich Chemical Co.

6. A 600 mm column with a 40 mm I. D. was used.

7. TLC analysis of the product was carried out on Quanta precoated silica gel, Q6 plates (developed with cyclohexane and visualized by charring with sulfuric acid) indicates a pure material. M^+ 370 ($C_{27}H_{46}$); $[\alpha]_D^{24}$ = + 19.6°; IR: 831, 783, and 678 cm^{-1}; NMR ($CDCl_3$), δ 0.66 (s, 3H, C-18 CH_3), 0.94 (s, 3H, C-19 CH_3), 5.23-5.75 (m, 2H, vinyl). The oily product crystallized after long standing, mp. 48-50°, lit.[3] 48-49°. The dibromo derivative, 3α,4β-dibromo-5β-cholestane melted at 98-99°, [lit. 98-100°: A. Nickon, N. Schwartz, J. Digiorgio and D. Widdowson, J. Org. Chem., 30, 1711 (1965).].

IMPROVED PROCEDURE FOR THE PREPARATION OF "OXAURACIL", 2H-1,3(3H)-OXAZINE-2,6-DIONE

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The 3-oxa derivative of uracil, 2H-1,3(3H)-oxazine-2,6-dione (I) has been under investigation as an antimetabolite due to its demonstrated activity vs. E. Coli[1] and L1210 leukemia cells.[2] Published procedures for the synthesis of I[3-5] suffer from low and irreproducible yields. The product obtained by heating maleic anhydride with trimethylsilyl azide to reflux in non-polar solvents is also usually severely contaminated with a difficultly separable brown polymer. Since we required large quantities of I in reasonable purity, a study of the optimum conditions for its synthesis was undertaken. A procedure for the synthesis of I in 60-80% yields with little polymeric contamination from trimethylsilyl azide and maleic anhydride in the absence of solvent has been developed.