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CONCERNING THE SYNTHESIS OF BUFALIN

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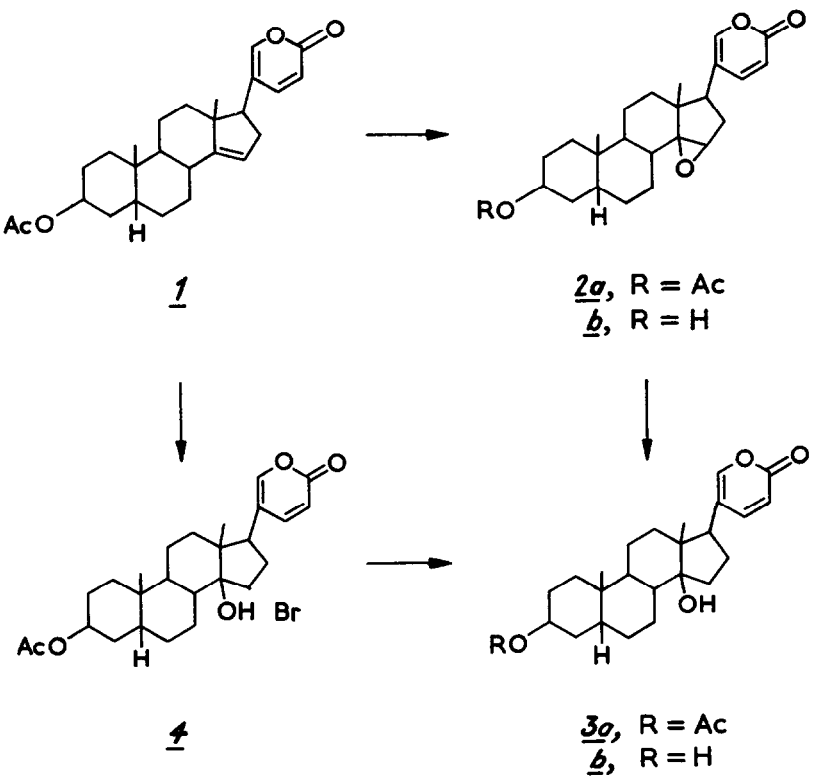
The last steps in the syntheses of bufalin (3b) by Sondheimer et al.[1] and by Pettit et al.[2] involve the conversion of 14-dehydrobufalin acetate (1) to resibufogenin acetate (2a) (by treatment of 1 successively with N-bromosuccinimide and basic alumina,[1] or with m-chloroperbenzoic acid [2]), followed by saponification to resibufogenin (2b) and reduction to (3b) with lithium aluminium hydride at low temperatures.[3] Very recently, Hauser et al.[4] reported that the low temperature reduction of resibufogenin does not lead to any detectable amount of bufalin. They concluded "Die Sondheimer'sche [1] und Pettit'sche [2] Bufadienolid-synthese endet demnach auf der Stufe des Resibufogenin, weil beide Arbeitskreise sich auf nicht reproduzierbare Patentangaben [3] verliesen."



1

2a, R = Ac
2b, R = H

4

3a, R = Ac
3b, R = H

We are unable to explain why the reduction of resibufogenin to bufalin could not be carried out by Hauser et al.[4] However, this apparently irreproducible step is unnecessary for the synthesis of bufalin. We have found that treatment of 14-dehydrobufalin acetate (1) with N-bromoacetamide in aqueous acetone, followed by reduction of the resulting bromohydrin (4) with Raney nickel [5] in methylene chloride, readily gave bufalin acetate (3a) Saponification with hydrochloric acid in methanol then yielded bufalin (3b), thus completing the synthesis [6]

EXPERIMENTAL

Bufalin (3b) from 14-dehydrobufalin acetate (1). N-Bromoacetamide (40 mg, 0 29 mmol) in water (0.6 ml) was added to 14-dehydrobufalin acetate (1) [1] (32 mg, 0.078 mmol) in acetone (3.4 ml) at 0°, and the mixture was stirred at 0° for 2 hr. The solvent was then evaporated (0.1 mm, 0°), and the resulting crude bromohydrin 4 in methylene chloride (4 ml) was added dropwise to a stirred suspension of pretreated [5b] Raney nickel (ca 1 2 g) in methylene chloride (2 ml) under nitrogen. The mixture was stirred at 15° for 4 hr, and then filtered through a short column of silica (Kieselgel GF_{254}). Preparative layer chromatography on silica, elution with ethanol-benzene (4 96), and crystallization from methanol-ether gave bufalin acetate (10.6 mg, 32%), mp 242-245°, identical (mixture mp, infrared spectrum) with an authentic sample (mp 242-246°).

A solution of bufalin acetate (10 mg) in methanol (10 ml) and 10% aqueous hydrochloric acid (10 ml) was allowed to stand at 20° for 48 hr Addition of water (20 ml) and saturated aqueous sodium hydrogen carbonate (30 ml), followed by extraction with ethyl acetate (20 ml), drying (magnesium sulphate), evaporation, and crystallization from methanol-ether, yielded bufalin (6.1 mg, 68%), mp 238-240°, identical (mixture mp, infrared spectrum) with an authentic sample (mp 239-242°).

REFERENCES AND NOTES

1. F. Sondheimer, W McCrae, and W.G. Salmond, J Amer. Chem Soc. 91, 1228 (1969).

2 G.R. Pettit, L.E. Houghton, J.C Knight, and F Bruschweiler, Chem. Commun. 93 (1970), J. Org Chem 35, 2895 (1970).

3. The reduction of resibufogenin to bufalin with lithium aluminium hydride at low temperatures was first described in the patent literature [H. Kondo and S. Ohno, U.S. Patent 3,134,772 (Chem. Abstr. 61, 5736f (1964)]

4. E. Hauser, H H.A. Linde, and S. Sprengel, Helv. Chim. Acta 55, 3026 (1972).

5. Inter al., see (a) M Heller, F.J. McEvoy, and S. Bernstein, Steroids 3, 193 (1964), (b) W Fritsch, H. Kohl, U Stache, W. Haede, K. Radscheit, and H. Ruschig, Ann 727, 110 (1969).

6. Since this work was completed, the conversion of 14-dehydrobufalin to bufalin by related methods has been reported in preliminary form by Y. Kamano and G.R. Pettit [J. Amer. Chem. Soc. 94, 8592 (1972)].