Tetrahedron Letters No.52, pp. 4495-4496, 1969. Pergamon Press. Printed in Great Britain

SYNTHESIS OF B-NOR-6-THIAEQUILENIN AND RELATED COMPOUNDS

R. R. Crenshaw and G. M. Luke

Research Division, Bristol Laboratories, Division of Bristol-Myers Company

Syracuse, New York, 13201

(Received in USA 17th September 1969: received in UK for publication 6th October 1969)

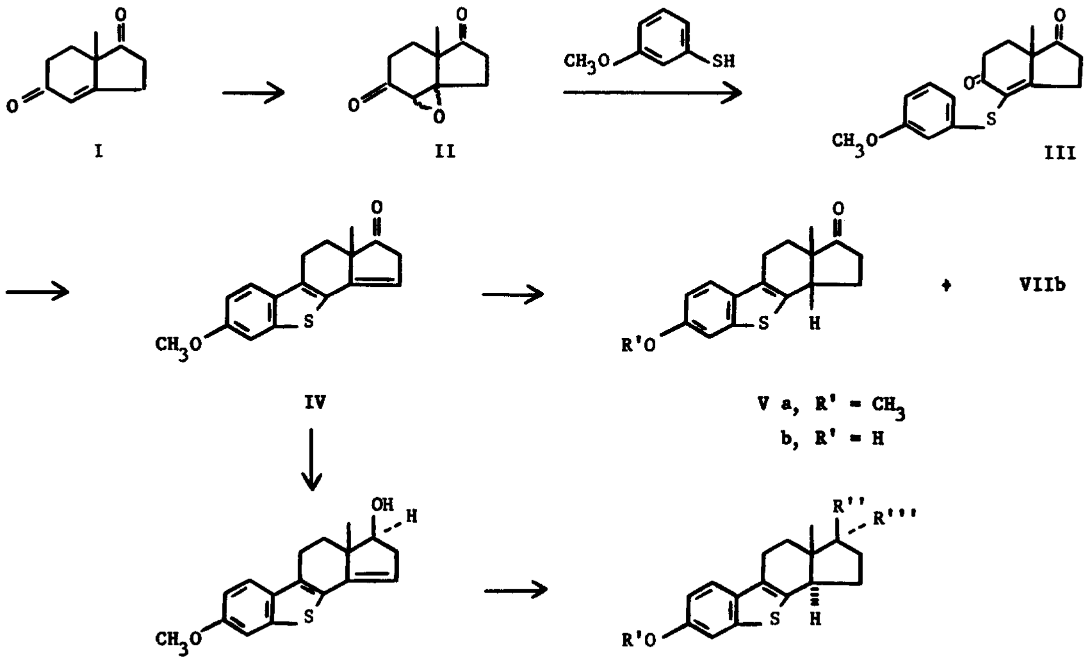
A synthesis of the ring B thiophene analog of 3-desoxyisoequilenin was first reported independently by Collins and Brown[1] and by Mitra and Tilak,[2a,b] the latter authors also claiming the corresponding analog of 3-desoxyequilenin. Tilak and co-workers have since reported an unsuccessful attempt at the synthesis of B-nor-6-thiaequilenin (VIIc),[2c] but recently have succeeded in the synthesis of the iso analog Vb.[2d] Generally, all of the reported syntheses have involved successive elaboration of rings C and D onto a benzo[b]thiophene. We now report a synthesis of VIIc starting with an hydrindene.

Alkaline hydrogen peroxide oxidation of I[3] produced the epoxide II (mp 77-79°). Condensation of *m*-methoxythiophenol (85% yield from *m*-methoxyphenylmagnesium bromide and sulfur) with II in refluxing DMF resulted in the dione III (mp 88.5-90°) in 80% yield. Cyclodehydration of III with $AlCl_3$ in CH_2Cl_2 gave a 60% yield of IV (mp 178-181°); uv $\lambda_{max}^{CH_3CN}$ nm(ϵ): 238 (18,300), 259 (11,100), 269 (11,600), 301 (26,700), 314 (23,300); nmr ($CDCl_3$) δ1.24 (s,C-CH_3), 5.96 (t,J=2.5 Hz,=$\overset{|}{C}$H).

Catalytic reduction (Pd/$CaCO_3$) of IV resulted in a mixture of Va and VIIb from which the pure *cis*-fused ketone Va (mp 138-139.5°) was obtained in 68% yield by fractional recrystallization; uv λ_{max}^{EtOH} nm(ϵ): 233 (28,600), 268 (10,100), 273 (9,950); nmr ($CDCl_3$) δ1.19 (s,C-CH_3). Demethylation of Va by fusion with pyridine hydrochloride gave *dl*-B-nor-6-thiaisoequilenin (Vb, mp 220-222°) in 61% yield.[4]

Sodium borohydride reduction of IV produced the β-alcohol VI (mp 179.5-181°) which was reduced catalytically to the C/D *trans*-fused alcohol VIIa (mp 160-161°); uv λ_{max}^{EtOH} nm(ϵ): 235 (34,700), 269 (10,800), 274 (10,700). Oxidation of VIIa according to the method of Pfitzner and Moffatt[5] gave the ketone VIIb (mp 145-147.5°); uv λ_{max}^{EtOH} nm(ϵ): 234 (27,400), 269 (9,550), 277 (9,450); nmr ($CDCl_3$) δ0.91 (d,J=0.6 Hz,C-CH_3). Fusion of VIIb with pyridine hydrochloride afforded *dl*-B-nor-6-thiaequilenin (VIIc, mp 260° dec) in 21% overall yield from IV. The corresponding β-alcohol (VIId, mp 224.5-227°) was prepared by demethylation (BBr_3/CH_2Cl_2) of VIIa.

The compounds described, all of which are racemates, gave satisfactory elemental and spectral (ir,nmr,uv) analyses. The β-alcohol configurations were assigned by analogy with the well-known stereochemical course of $NaBH_4$ reductions on 17-ketosteroids. The C/D fusion assignments were made on the basis of precise measurements of the relative chemical shifts of the angular methyl protons in Va and VIIb, the latter showing the methyl resonance at higher field and thus being assigned the *trans*-fused configuration.[6] These assignments are further substantiated by a splitting of the angular methyl protons seen in VIIb which is absent in the *cis*-fused Va.[7]



V a, R' = CH_3
b, R' = H

VII a, R' = CH_3; R'' = OH; R''' = H
b, R' = CH_3; R'', R''' = O
c, R' = H; R'', R''' = O
d, R' = H; R'' = OH; R''' = H

Acknowledgment.--The authors wish to thank Mr. A. L. Vulcano for 100 MHz nmr data.

References

1. R.J. Collins and E.V. Brown, J. Am. Chem. Soc., 79, 1103 (1957).
2. (a) R.B. Mitra and B.D. Tilak, J. Sci. Ind. Res., 14B, 132 (1955); (b) R.B. Mitra and B.D. Tilak, ibid., 15B, 497 (1956); (c) M.K. Bhattacharjee, R.B. Mitra, B.D. Tilak and M.R. Venkiteswaren, Tetrahedron, 10, 215 (1960); (d) B.D. Tilak and M.K. Bhattacharjee, Indian J. Chem., 7, 36 (1969).
3. C.B.C. Boyce and J.S. Whitehurst, J. Chem. Soc., 2022 (1959).
4. Reference 2(d) reports this compound as an oil, bp 170-75° (0.02 mm).
5. K.E. Pfitzner and J.G. Moffatt, J. Am. Chem. Soc., 87, 5670 (1965).
6. N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, Inc., San Francisco, 1964, Ch. 2.
7. Cf. C.W. Shoppee, F.P. Johnson, R.E. Lack, J.S. Shannon and Š. Sternhell, Tetrahedron, Suppl. No. 8, Part II, 421 (1966), and references cited therein.