Tetrahedron Letters No.29, pp. 2763-2765, 1967. Pergamon Press Ltd. Printed in Great Britain.

NEW TOTAL SYNTHESES OF (±)-EQUILENIN METHYL ETHER AND (±)-ISOEQUILENIN METHYL ETHER: SOME REMARKS ON POLYPHOSPHORIC ACID CYCLISATIONS

A. J. Birch and G. S. R. Subba Rao
Department of Chemistry, University of Manchester

(Received 15 May 1967)

A simple synthesis of the cyclopentenophenanthrene nucleus with a steroid pattern of oxygenation involves the intermediate (1).[1] This can be cyclised directly to (2). After reduction of (1) to (3; R = H) it gives rise to (4; R = H). The drawback to the first course is that the ring-system is difficult to hydrogenate appropriately[2] and to the second course that the product (5; R = H) of hydrogenation of (4; R = H) gives only isoequilenin methyl ether (5; R = Me) on angular-methylation.[3]

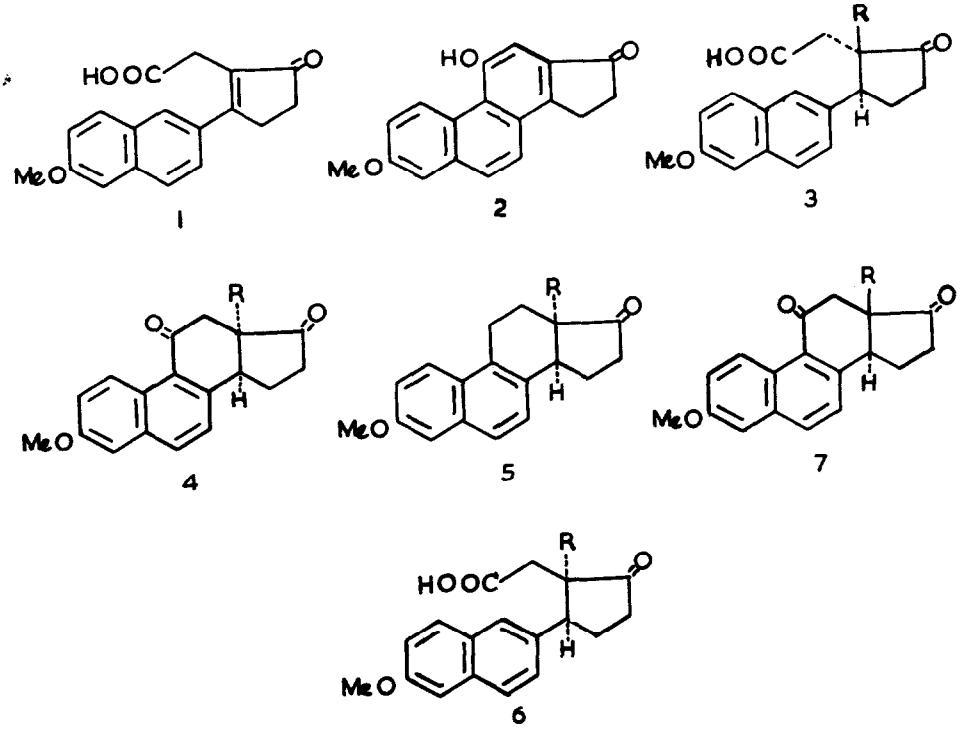
Reduction of (1) with lithium in liquid ammonia gave, as expected from similar reactions,[4] the correct enolate-anion for angular methylation, since addition of methyl iodide gave a mixture of (3; R = Me) and (6; R = Me) as a gum, m/e 312, with the expected spectra. The mixed methyl ester was shown by g.l.c. to be a mixture of the esters of (6; R = Me) (25%) and (3; R = Me) (75%).

The mixture of acids was cyclised with phosphorus oxychloride, phosphoric oxide and phosphoric acid. The neutral product (30% yield) was chromatographed on neutral alumina to give the dione (4; R = Me) (10%) m.p. 158-160°, $\lambda_{max.}$ 245, 314 mμ (ε 12250, 2300); $\nu_{max.}$ 1735, 1665, 1620 cm.$^{-1}$; τ 0.75d (J = 9 c.p.s.) (1H); 2.1d (J = 9 c.p.s.) (1H); 2.6 - 2.9m (3H); 6.1s (3H); 6.7 - 8.0m (7H); 8.75s (3H); m/e 294, and also the dione (7; R = Me) (85%) m.p. 195-196°, $\lambda_{max.}$ 245, 315 mμ (ε 13500, 2500); $\nu_{max.}$ 1740, 1675, 1620 cm.$^{-1}$; τ 0.8d (1H); 2.1d (1H); 2.6 - 3.0m (3H); 6.15s (3H); 6.7 ; 8.0m (7H); 8.75s (3H); m/e 294. The diones were hydrogenated with palladium-platinum on acidic charcoal[5] to give respectively (±)-isoequilenin methyl ether, m.p. 120-124° (lit.[6] m.p. 125-127°), agreeing with reported spectra, and (±)-equilenin methyl ether[7] m.p. 188-189° (undepressed by an authentic specimen), $\lambda_{max.}$ 268, 278, 289, 323, 337 mμ (ε 4500, 4700, 3250, 2000, 2400); $\nu_{max.}$ 1730, 1625, 1600 cm.$^{-1}$.

The cyclisation of (3; R = Me) with recycling of recovered acid gives about 40% yield and is the least satisfactory stage. For reasons not clear, it is a difficult process, and polyphosphoric acid was originally devised as the only reagent capable of producing cyclisation of (3; R = H) leading to our general proposal of this reagent for cyclising arylbutyric and arylpropionic acids.[3] The reagent used was phosphoric oxide in phosphoric acid. Later[8] Snyder and Werber made a similar proposal based initially on the

use of partially hydrolysed phosphorus oxychloride, and despite some initial indications[8] it has not been appreciated that these reagents may behave rather differently. We find, for example, that while polyphosphoric acid by the standard technique[3] gives about 55% yield of 5-methoxyhydrindone from 3-methoxyphenylpropionic acid a modified technique gives higher yields. If this acid (1 g.) is dissolved in phosphorus oxychloride (5 ml.), added to syrupy phosphoric acid (5 ml.) and phosphoric oxide (5 g.) added with stirring, the temperature remains at about 100° because of refluxing of the phosphorus oxychloride. After 1.5 min. the mixture is added to water and the ketone recovered, giving an 85% yield of recrystallised product, m.p. 110°. The acid chloride may be an intermediate.

The original[3] procedure on (3; R = Me) leads to yields of 15-30%, but these are critically dependent on exact conditions and are not easily reproducible. The altered method gives reproducible yields of about 30% with 25% of recovered acid.



Acknowledgements

We are indebted to Dr. Herchel Smith of Wyeth Laboratories Inc. for an authentic specimen of (±)-equilenin methyl ether, and to the Australian National University for a Research Fellowship (G. S. R. S. R.)

References

1. R. Robinson, J. Chem. Soc. 1396 (1938); R. Robinson and H. N. Rydon, ibid. 1394 (1939).
2. A. J. Birch and G. S. R. Subba Rao, Tetrahedron Letters, 857 (1967).
3. A. J. Birch, R. H. Jaeger and R. Robinson, ibid, 582 (1945).
4. G. Stork, P. Rosen, N. Goldman, R. V. Coombs and J. Tsuji, J. Amer. Chem. Soc. 87, 275 (1965).
5. N. D. Zelinsky, K. Packendorff and L. Leder-Packendorff, Ber. 66, 872 (1933).
6. W. E. Bachmann, W. Cole and A. L. Wilds, J. Amer. Chem. Soc. 62, 824 (1940).
7. W. S. Johnson, J. W. Peterson and C. D. Grutsche, ibid. 69, 2942 (1947).
8. H. R. Snyder and F. X. Werber, ibid. 72, 2962 (1950).