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THE UNUSUAL COURSE OF THE REACTION OF 3β-ACETOXYLANOST-5-EN-7-ONE WITH p-TOLUENESULPHONYLHYDRAZINE

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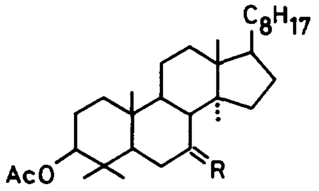
Summary: During the attempted preparation of the p-toluenesulphonylhydrazone of enone 2a it has been established that a reductive side reaction occurs - probably brought about by di-imide, arising from the thermal decomposition of p-toluenesulphonylhydrazine.

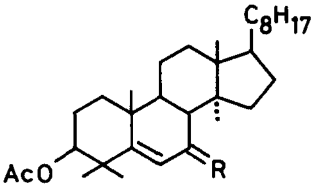
In connection with our studies[1] directed towards the photochemistry of lanostadiene derivatives, we sought an improved route to 3β-acetoxylanosta-5,7-diene (3) which would be readily applicable to formation of a hitherto unknown lanostane analogue of vitamin D_3. A four step synthesis of diene 3 was described by Barton and Thomas[2] starting from 7-ketone 1a but the overall yield was only 11%. Thus, reduction of enone 2a, obtained by SeO_2 oxidation of 1a, with $LiAlH_4$ followed by acid-catalyzed dehydration and re-acetylation afforded 3. Since the yield of the first step (1a → 2a) was excellent, we were encouraged to examine a different approach for the conversion of 2a to 3 through a modified Bamford-Stevens reaction[3] of the tosylhydrazone derivative of 2a.

The α,β-unsaturated ketone 2a[4] ($[\alpha]_D^{24}$ -34.4°, $CHCl_3$, m.p. 191-192°C; lit[2]: m.p. 188-189°C, $[\alpha]_D$ -37°, $CHCl_3$) was obtained by oxidation of 1a according to the procedure of Barton and Thomas[2]. In our hands however the reaction failed to provide 80% yield of 2a as reported by the authors and we obtained two by-products 4 and 5 in respective yields of 20% and 25%. The known[5] trienone 5 (m.p. 196-198°C, $[\alpha]_D^{24}$ +61.2°, $CHCl_3$) was isolated by column chromatography on silica-gel, but 8β-hydroxyketone 4 could only be separated from 2a by fractional crystallization[6].

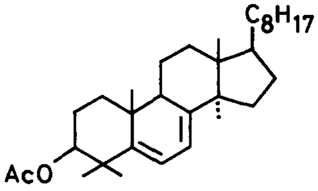
The structural assignment of 4 (m.p. 171-173°C, $[\alpha]_D^{24}$ -15.1°, $CHCl_3$) is based both upon spectral data[7] and a mechanistic rationale. A comparison of ^{13}C-NMR spectra of 2a[9] and 4 was particularly informative. Considerable deshielding effects observed in 4 for C-8 ($\Delta\delta$=29.7 ppm), C-18 ($\Delta\delta$=2.3 ppm) and C-19 ($\Delta\delta$=5.1 ppm) strongly supported the presence of an 8β-hydroxyl moiety.



1a R=O
1b R=NNHTs



2a R=O
2b R=NNHTs



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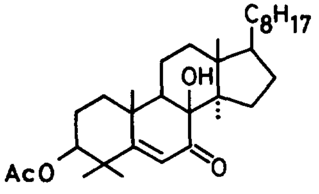

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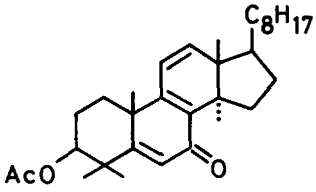

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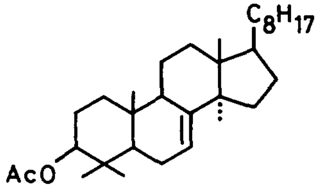

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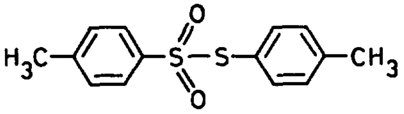

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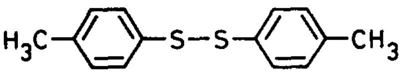

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The reaction of enone 2a with tosylhydrazine [10] was initially performed in protic solvents as recommended[3]. The starting compound 2a was recovered unchanged after prolonged (up to 20 hrs) reflux with tosylhydrazine in methanol or acetic acid. The only observable process, which occurred in ethanol containing traces of HCl, was the steady hydrolysis of the 3β-acetate moiety. Upon further investigation, it was realized that the choice of solvent was critical to the course of the reaction. Whilst an unseparable, complex mixture of products was obtained when the reaction was carried out in n-butanol (2 hrs), these problems were not in evidence when the aprotic solvent toluene was used. In the latter case, the reaction (2 hrs) resulted in the build up of a major, polar product 1b (40%) which was separated from the unreacted 2a (30%) by column chromatography on silica-gel. We have found that prolonged heating resulted in considerably diminished yields of 1b. The fairly unstable tosylhydrazone 1b (m.p. 187-192°C, dec.) was shown to be identical with the substance prepared by the reaction of 7-ketone 1a with tosylhydrazine in refluxing toluene. Treatment of 1b (1 mmol) with LiH (1 g) in toluene (20 ccm) at reflux for 1 h gave after chromatographic purification the expected 3β-acetoxylanost-7-ene (6; m.p. 146-147°C), which was shown to be identical with an authentic specimen[11].

The unexpected reduction of the C_5-C_6 double bond in 2a and/or 2b[12] could be explained by assuming that under the reaction conditions di-imide was generated. This, in turn, implies that the thermal decomposition of tosylhydrazine occurs under milder conditions than those previously described[13]. Such an explanation was further supported by the fact that sulphur-containing aromatic by-products 7 (m.p. 76-77°C; lit[14]: m. p. 76°C) and 8 (m.p. 45.5-46°C; lit[15]. m.p. 45-46°C) were usually isolated, in variable amounts, from the large scale reactions of 2a with tosylhydrazine.

Blank experiments, performed in the absence of steroid[16], showed that a slow decomposition of tosylhydrazine occurs also even at 80°C. Increase in the temperature of reaction markedly enhanced the decomposition rate and favoured the formation of disulfide 8. In a polar solvent (n-butanol) the thermolysis is a relatively slow process and the presence of hydrazine[17] in the reaction mixture has been established according to the method of Pesez and Pettit[18]. It is likely therefore, that the reduction of 7 with hydrazine accounts, to some extent, for the enhanced proportion of disulfide 8 in the extracted neutral products. We have confirmed that the reaction of thiosulphonate 7 with hydrazine proceeds smoothly under the reaction conditions to give disulfide 8 as the sole product.

In conclusion, we have demonstrated that the p-toluenesulphonylhydrazone derivatives of unreactive ketones may be prepared in toluene, provided that no function is present in the molecule which may undergo reduction with di-imide. It is also worthy of note that this work lays open an attractive possibility for the three step conversion of commonly available steroidal 5-enes into the isomeric Δ^7-olefins *via* intermediate 7-keto tosylhydrazones.

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References and Notes

1) Jagodziński J.J., Siciński R.R., Tetrahedron Letters, (1981).
2) Barton D.H.R., Thomas B.R., J. Chem. Soc., 1842 (1953).
3) Shapiro R.H., 'Organic Reactions', vol. 23, chapter 3; J.Wiley and Sons, Inc., 1976.
4) All compounds described in this work have the appropriate spectral properties and the required composition by elemental analyses.
5) Birchenough M.J., McGhie J.F., J. Chem. Soc., 1249 (1950).
6) The attempted separation of 2a and 4 (possessing the same mobility in TLC) by column chromatography failed.
7) 8β-Hydroxyenone 4 IR, ν_{max}: 3581, 1731, 1663, 1611, 1263 cm^{-1}; UV, λ_{max}. 238.5 nm (ε 13300); ^{1}H-NMR, δ, ppm 2.09 (s, 3β-OAc), 4.62 (m, 3α-H), 6.00 (s, 6-H) ^{13}C-NMR[8], δ, ppm: 36.3 (C-1),

23.2 (C-2), 77.7 (C-3), 41.8 (C-4), 176.0 (C-5), 123.7 (C-6), 200.7 (C-7), 79.4 (C-8), 47.8 (C-9), 37.8 (C-10), 18.4 (C-11), 28.3 (C-12), 46.4 (C-13), 50.7 (C-14), 33.4 (C-15), 28.3 (C-16), 50.1 (C-17), 17.3 (C-18), 22.4 (C-19), 35.3 (C-20), 18.2 (C-21), 36.3 (C-22), 24.1 (C-23), 39.5 (C-24), 28.0 (C-25), 22.8 (C-26), 22.6 (C-27), 21.5 (C-30), 24.1 (C-31), 26.2 (C-32), 21.2 and 170.5 (acetate).

8) Assignments were made by combination of ND and SFORD techniques, cross-correlations with spectra of respective 3β-CH and 3-oxo derivatives as well as by analogy with assignments in ^{13}C-NMR spectra of related systems.

9) Enone 2a: ^{13}C-NMR[8], δ, ppm 35.1 (C-1), 23.4 (C-2), 77.6 (C-3), 41.1 (C-4), 175.1 (C-5), 126.0 (C-6), 203.0 (C-7), 49.7 (C-8), 45.4 (C-9), 38.4 (C-10), 20.4 (C-11), 31.8 (C-12), 45.9 (C-13), 47.2 (C-14), 34.8 (C-15), 28.3 (C-16), 49.6 (C-17), 14.9 (C-18), 17.4 (C-19), 36.1 (C-20), 18.8 (C-21), 36.6 (C-22), 24.1 (C-23), 39.5 (C-24), 28.0 (C-25), 22.8 (C-26), 22.6 (C-27), 19.4 (C-30), 24.6 (C-31), 26.0 (C-32), 21.2 and 170.5 (acetate).

10) In all experiments enone 2a (1 mmole) and p-toluenesulphonylhydrazine (6 mmole) were refluxed in the solvent specified in the text (in each case 10 ccm).

11) Shoppee C. W., Call J. C., Lack R. E., J. Chem. Soc., C, 1581 (1968).

12) In view of the absence (^{1}H-NMR and TLC control) of any detectable amount of the possible intermediates 1a and 2b in the reaction mixture, the path leading to 1b has not been elucidated.

13) Dewey R. S., van Tamelen E. E., J. Amer. Chem. Soc., 83, 3729 (1961).

14) Harrison P. W. B., Kenyon J., Phillips H., J. Chem. Soc., 2085 (1926).

15) Schonberg A., Schutz O., Bruckner V., Peter J., Berichte, 62, 2560 (1929).

16) p-Toluenesulphonylhydrazine (1g) was dissolved in the solvent (10 ccm), specified in the text and the solution was refluxed for a) 20 hrs (benzene, 80°C), b) 2 hrs (toluene, 120°C), c) 2 hrs (p-xylene, 140°C) and d) 10 hrs (n-butanol, 117°C). From the crude products the respective neutral fractions were isolated a) 0.03g, b) 0.5g, c) 0.6g and d) 0.1g. The approximate ratios of 7 to 8 were found as· a) 10 1, b) 4 1, c) 2 1 and d) 1 1, respectively.

17) Detectable amounts of hydrazine were also present in the refluxing ethanolic solution (Chang F. C., J. Crg. Chem., 30, 2053 (1965)).

18) Pesez M., Pettit A., Bull. Soc. Chim. France, 122 (1947).

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